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FORMULATION AND EVALUATION OF NANOPARTICULATE MATRIX TABLET OF CANDESARTAN

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Abstract : Candesartan, an angiotensin II receptor antagonist, is used to treat hypertension and heart failure. However, its poor solubility and bioavailability limit its therapeutic efficacy. This study aimed to develop nanoparticulate matrix tablets of Candesartan to improve its dissolution rate and bioavailability. Nanoparticles of Candesartan were prepared using a suitable method and incorporated into matrix tablets using polymers. The formulated tablets were evaluated for their physicochemical properties, in vitro drug release, and in vivo pharmacokinetic performance. The results showed that the nanoparticulate matrix tablets significantly improved the dissolution rate and bioavailability of Candesartan compared to conventional tablets. The optimized formulation exhibited a sustained release profile and improved therapeutic efficacy. These findings suggest that nanoparticulate matrix tablets of Candesartan could be a promising approach for enhancing the treatment of hypertension and heart failure.

1) INTRODUCTION

For a long time, Of all the techniques used for the delivery of drugs through different pharmaceutical products in different dosage forms, orally drug administration was the most often used way of administration.. Due to its ease of administration and cheap cost of therapy, oral administration is the most conventional and straightforward method of administering dose forms, which increases patient compliance. Approximately 50% of pharmaceutical medications on the market are taken orally, with tablets being the most often used dosage type.

The primary goal of creating a dosage form it to deliver the entire quantity of medication in the appropriate form to the designated site and carry out its pharmacological effect. The overall chemical composition of a solid unit dosage, tablet manufacturing procedure, and dosage form design all have an impact on the drug's productivity. A complete dosage form contains a number of excipients, the most important of which is the active medicinal component. Since a single API cannot provide a decent formulation, the other ingredients are crucial to creating an appropriate dose form. The main active component can combine with other components during the blending process when the excipients and medicine are mixed, so it's critical to follow a certain protocol when constructing the unit dosage form.

2) Nanoparticulate Drug-Delivery Systems:

In an effort to address drug delivery concerns, nanoparticulate drug-delivery systems, or NPDDSs, are being investigated. The NPDDs have well-defined areas for the purpose of releasing and targeting medicinal substances. These vehicles can eliminate or at least lessen a number of problems associated with drug trafficking. There are numerous instances of toxicity difficulties with excipients designed to prevent drug aggregation, and many medications suffer from precipitation problems at high concentrations due to their hydrophobic regions.

Different kinds of medication delivery systems using nanoparticles:

A. Nanoparticles of solid lipids

Try to formulate Increased drug stability, high drug payload, no carrier toxicity, avoiding organic solvents, and incorporating a lipophilic and aqueous drug matrix are all benefits of solid lipid nanoparticles.

B. Nanosuspension
C. Dendrimers
D. Proliposomes

3) Drug delivery system of the matrix type

These are the controlled drug delivery methods that release the drug continually, such diffusion-controlled and dissolution-controlled procedures. To regulate the release of the medicines, which have different solubility properties, the drug is distributed in swellable aqueous compounds, a matrix made up of solid non-swellable hydrophobic substances, or plastic materials

One of the simplest techniques for creating long-lasting release dosage forms involves directly compressing a mixture of medication, retardant, and excipients to create a tablet that introduces the medication within a retardant matrix. The medication and suppressant powder blended mixture is granulated prior to compression. In the formulation of matrix systems, hydrophilic & hydrophobic polymers are the most often utilized components. Hydroxypropylmethyl cellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), xanthan gum, sodium alginate, Poly (ethylene oxide), and cross-linked homopolymers and copolymers of acrylic acid are examples of commonly available hydrophilic polymers. It is usually given in micronized forms because a tiny particle size inhibits the development of a viscous coating on the tablet's surface.

A sustained-release (SR) kind of matrices tablet has created a new path for innovative drug delivery technologies (NDDS) in the pharmaceutical technology sector. During the manufacturing process, it minimizes important production processes like coating and pelletization. Additionally, it lowers the rate of drug release from the dosage form, which is mostly controlled by the kind and quantity of polymer utilized in the formulations. The majority of SR dosage forms are prepared using a hydrophilic polymer matrix.

MatrixTablets:

One of the most complex processes for producing dosage forms with modified release involves directly compressing a combination of medication, retardant, and excipients to create a tablet with the medication embedded in a retardant matrix. However, a combination of medication and retardant may be used before to compression.

a) Hypertension :

A novel class of antihypertensive medications is indicated by the receptors for angiotensin II antagonists (ARBs). ACE inhibitors, which similarly affect the rennin-angiotensin system, work in a different way than they do.

The pathophysiology of required high blood pressure, reno-vascular congestive heart failure, hypertension, and renal disorders associated with albuminuria is influenced by the rennin-angiotensin system, particularly angiotensin II. . These disorders have been successfully treated by blocking the rennin-angiotensin pathway with ACE inhibitors; yet, a number of ACE drug side effects are unrelated to the angiotensin II blockage. [12]

Candesartan is the medication candidate chosen for the trial. It is an antagonist of the angiotensin II receptor that is used to treat hypertension. One BCS Class II medication is candesartan. Because of their limited solubility and metabolic breakdown, these substances have low bioavailability. With a dose of 16 mg, candesartan has an oral bioavailability of up to 15%. It has a 5–9 biological half-life.

1) Novel Drug Delivery System :

One of the key ways that they are adapting to the problems associated with drug bioavailability is through the development of novel drug delivery systems. It is the speed and degree to which a medication becomes accessible to the intended recipient following oral delivery. Because only a tiny portion of the provided dose is absorbed inside the blood stream and ready to be delivered to the target location, the majority of the most recent medications possess poor bioavailability and must be taken at greater doses. Drug delivery systems that are self-microemulsifying and self-nanoemulsifying, nano suspensions, nano fluid emulsion polymeric nanoparticles, solid lipid nanoparticles, and vesicular delivery vehicles like niosomes and liposomes, among others. Because of their tardy start to action while low oral bioavailability and lack of dose proportionality, failure to maintain normal the plasma levels, as well as side effects, medicines that have low solubility have an influence on their formulation when employing traditional processes.Therefore, using standard dosage forms could result in either too much or too little medication, as well as poor patient compliance. These difficulties are also addressed by developing innovative drug delivery methods that offer advantages like decreased dosage frequency, decreased dosage size, targeted targeting, enhanced porosity, and improved oral bioavailability.

When it comes to developing drug delivery systems for powerful medications whose clinical development failed due to poor solubility, lack of permeability, insufficient its bioavailability and other weak biopharmaceutical qualities, nanotechnology is an extremely effective and successful technique.

Thanks to interdisciplinary support from academics in academia, industry, and the federal government, nanotechnology is a rapidly growing discipline. By making this possible, nanotechnology plays a critical role in future therapies as nanomedicines, reducing the dosages needed for efficacy and improving therapeutic index and safety aspects of novel treatments.

Regarding size restrictions, nanotechnology is defined by the National Nanotechnology Initiative (NNI) as having dimensions of typically 1 to 100 nanometers (nm), while it can be expanded to 1000 nm in the border range. This range of particles appears to be ideal for achieving several crucial functions as nano-carriers, including changing a drug's electrical characteristics, reactivity,

strength, and, eventually, behavior in vivo. There are good ideas for creating novel nano delivery methods for medications that are now on the market, particularly cancer treatments. Researchers are working on developing nanotechnology to be capable to deliver the drug to the focused on tissue, discharge the drug at a regulated rates, have a reusable drug delivery structure, and be able to be eliminated from the body's degradation processes by utilizing the use of nanotechnology in the design of drugs and delivery.From being only a component of the pharmaceutical manufacturing process, drug delivery systems have evolved into a catalyst for innovation and financial success. By using innovative drug delivery systems

(DDSs), the pharmaceutical industry can increase patent protection and introduce new treatments to the market. Any drug delivery system's goal is to deliver a therapeutic dose of medication to the body's location in a timely manner while preserving the appropriate levels of the drug in the bloodstream. The DDS's idealized goal identifies two main factors, such as the drug's temporal and geographical delivery. Drug selection and distribution at the appropriate location at the chosen time point are made possible by the application of nanoscale DDSs, opening up new avenues for drug therapy. Drugs can be added to solid lipid nanoparticles (SLN), liposomes, surfactant, lipid-modified hydrogels, (biodegradable) polymeric nanoparticles, or intricate non-viral gene transfection systems to accomplish this. One significant benefit of formulations is that they increase the amount of medicine that this system can absorb; this is significant for reasons relating to manufacturing costs as well as adverse effects connected to carriers.

4.1 Advantages of New drug delivery system :

1. Discuss both chemical and physical deterioration.
2. Long-term delivery.
3. The spread of tissue macrophages has increased.
4. An improvement in steadiness.
5. Pharmacological action is increased.
6. defense against toxicity.
7. The bioavailability has increased.
8. Improvement in solubility

4.2 Drug delivery and nanostructures:

Proteins, polysaccharides, and synthetic polymers are among the components that can be used to create drug delivery nanoparticles. Numerous factors influence the choice of material, including the size of the nanoparticles, the drug's intrinsic properties, surface properties including charge and permeability, and the degree of biodegradability.

Liposomes, Dendrimers ,Solid lipid nanoparticles, Polymeric Micelles, Gold nanoparticles , Nanotubes, Nanocrystals, Nanofibers, Quantum dots

4.3 TYPES OF NOVEL DRUG DELIVERY SYSTEM

Nano suspensions:

Self-emulsifying, Self-micro emulsifying (SMEDDS) and Self-nano emulsifying (SNEDDS) drug delivery system:

Self-Emulsifying:

Solidification Technique for converting Liquid SEDDS to Solid-SEDDS

Nanoemulsions:

Solid lipid nanoparticle

4.4 NANOPARTICLES:

Particles with different shapes but at least a single dimension in the nanoscale—which should be less than 100 nanometers—are referred to as nanoparticles. Numerous advantages of this drug delivery method include improved bioavailability, longer drug half-life, and the ability to overcome off-target toxicity. A multifunctional mix of an active medicinal component and selectively targeted molecules makes up the innovative form of therapeutic nanoparticle. Imaging agents that enable localization using conventional x-ray, magnetic resonance, or positron emission tomography, or PET, methods are frequently used. Mesoporous silicon nanoparticles are used to distribute hydrophilic or hydrophobic molecules that are active in a regulated manner. Sufficient advancements in MSN surface characteristics, such as PEGylation and surface functionalization, make them an appropriate drug delivery system for the treatment of cancer. A crucial step in assisting the creation of new therapies for clinical practice is the use of polymer systems, which offer a great deal of freedom in the modification and optimizing of nano carriers. Nano capsules are systems where the medicine is encased in a particular polymeric membrane, while nanotechnology spheres are matrix systems where the medication

is uniformly distributed. The classification, preparation method, characterization, application, and health perspective are provided by this systematic review.

4.5 Techniques for creating nanoparticles

High and regulated quality high-throughput NPs are essential for commercialization in several application areas. The top-down technique, which begins synthesis with the bulk equivalent and systematically drains off bit by bit to produce fine NPs, is one of the two main plans that are frequently employed to prepare NPs. The most popular top-down techniques for producing large quantities of NPs include photolithography, or electron microscope lithography, which milling methods, the anodization, ions and plasma etching; (b) the bottom-up strategy, which creates a range of NPs by putting atoms and molecules together. self-assembly of monomer/polymer molecules,chemicals or electrochemical nanostructural the process of precipitation sol-gel processing, laser a process called chemically vaporized deposition (CVD), plasma or flames spraying synthesis, and bio-assisted synthesis are a few examples of the bottom-up technique.

4.6 Physical techniques for creating nanoparticles

Mechanical pressure, high-energy radiations, thermal energy, or electrical energy are used in the physical formulation of nanoparticles and are in charge of material abrasion, melting, evaporation, and condensation. These techniques, which mostly use a top-down methodology, are advantageous since they produce comparable monodispersed NPs and are solvent-free. Physical techniques are also low cost cause to substantial waste generated while sysntheis are done. High-energies grinding with balls, laser sterilization, electrical spraying, inert gases condensate to physically vapour accumulation, laser a process called flash spray pyrolysis, and melt mixing are some of the most often used physical techniques for producing nanoparticles.

a) HEBM. That is ball mill with high enegry

b) IGC, or gas condensation inerty

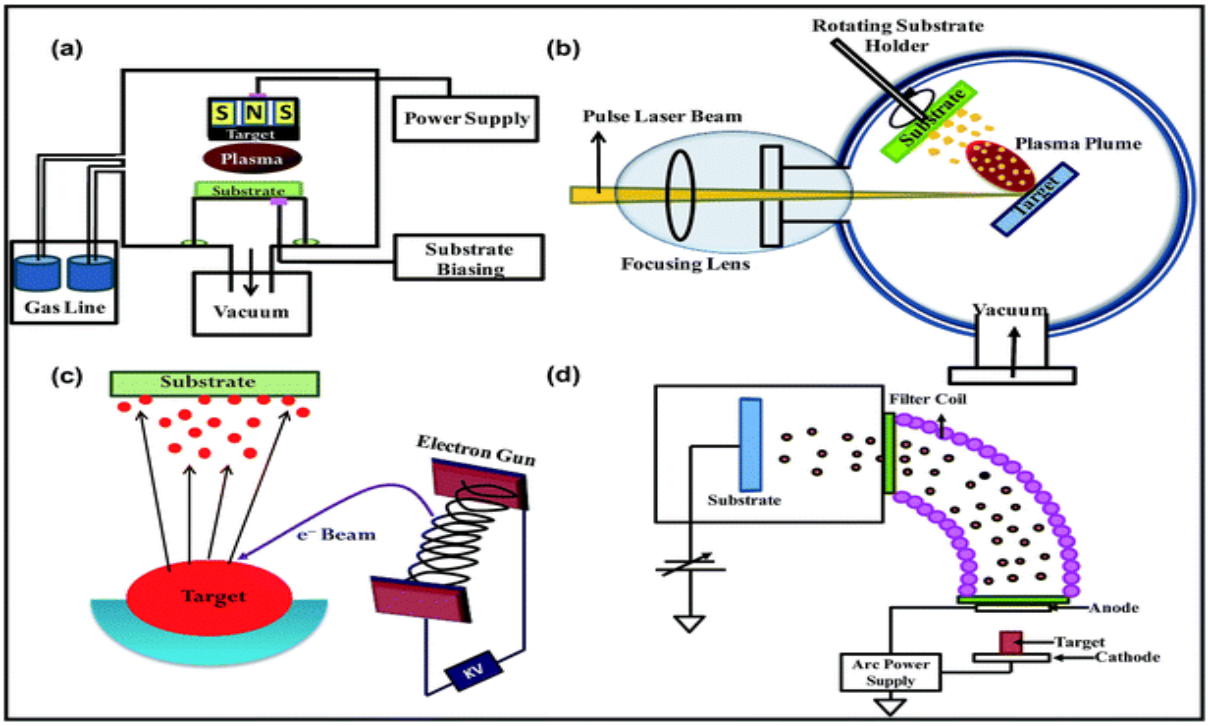
c) PVD

For the synthesis of NPs, the most used PVD techniques are i) Sputtering, ii) electron beam evaporation, iii) pulsed lasers deposition, and arc vacuum are the first four methods. Pyrolysis via laser.

- Pyrolysis by flame spray (FSP).

- method of electrospraying.

- melting and mixing.



4.7 Chemical techniques for creating nanoparticles:

i) Sol-gel technique.

ii) The microemulsion method.

Hydrothermal synthesis (iii).

iv) Synthesis of polyols.

v) Chemical Vapor Synthesis (CVS) and Chemical Vapor Deposition (CVD**).**

vi) Chemical vapour deposition enhanced by plasma (PECVD).

Bio-assisted techniques for nanoparticle production

NPs can be formed and manufactured using an environmentally safe, low-toxic, economical, and effective process thanks to bioassisted techniques, biosynthesis, or green synthesis. These approach uses organisms like bacteria, fungus, infectious agents, yeast, microorganisms extracts from plants, etc. for the manufacture of metal and metallic oxide NPs. Three types of bioassisted techniques can be distinguished:

(i) Biogenic synthesis using microorganisms (ii) Biogenic synthesis using biomolecule-based templates (iii) Biogenic synthesis based on plant extract

Vii) using microbes for biogenic synthesis.

For the production of NPs, prokaryotic bacteria, actinomycetes, fungus, algae, and yeast are the most common bio-reactors. This approach of making a Nanoparticles with certain range (TiO2, Ag, , and zinc and Au etc.) was designed through extensive scientific research. Microorganisms take up target ions in their surroundings and use enzymes produced by cellular processes to convert the metallic ions into the corresponding metal. The place of NP synthesis determines whether this synthesis is intracellular or extracellular. In the intracellular approach, In the presence of enzymes, metal ions are transferred within the microbial cell to produce. NPs. Metal ion trapping on cell surfaces and ion reduction in presence of enzymes, which happens during nanoparticle formation

viii) Nanoparticles are designed using biomolecules as templates.

NPs were created using a variety of biomolecules as templates, including viruses, membranes, diatoms, and nucleic acids. An improved biomolecular template with a close bond to transition metal ions is DNA. It was demonstrated that before adding transition- metal ions (such as gold or Au(III) metallic ions) to DNA macromolecules, which ultimately leads to the synthesis of Au NPs, DNA hydrogel could be prepared and crosslinked. Au(III) is reduced during the process, producing aluminum atoms and clusters of metals that grow into NPs of Au on the genetic chain.

ix) plant extracts for the production of nanoparticles.

One of the most efficient, quick, safe, non-toxic, and environmentally beneficial ways to produce NPs is through the biosynthesis of plant extracts or biomass. This process has mostly been used to create NPs of metal oxides, noble metals, bi-metallic alloys, etc.

4.8 Features of the nanoparticle :

A nanoparticle's potential and applicability are indicated by its distinctive feature. Several measuring techniques are used to characterize the nanoparticles.

-Size

Characterization of nanoparticles is a common and significant measurement method. It determines the particle's size, dispersion, and whether it falls within the nano or microscale range. The most used method for measuring particle size and dispersion is electron microscopy. Particles and bunches are measured using the images of electron scanning microscopes (SEM) and transmitted electron microscopes (TEM), whereas samples that are in the solid phase are analyzed using laser diffraction methods.

Centrifugation and photon correlation spectroscopy are used to measure the particles in the liquid phase. A Scanning Mobility Particles Sizer (SMPS), which provides faster and more accurate measurements than other methods, is employed since the particles in the gaseous phase are crucial and irreverent to imaging techniques.

-Charge on the surface

A nanoparticle's interactions with a target are determined by its charge or surface charge. Surface charges and their distribution and constancy in a solution are often measured using a zeta potentiometer. The charge of nanoparticles in the gaseous phase is determined using a Differential Mobility Analyzer (DMA).

-Area of the surface

Another crucial element in the characterization of nanoparticles is their surface area. A nanoparticle's performance and characteristics are greatly influenced by its outermost layer area to volume ratio. BET analysis is the most widely used method for measuring surface area. For a surface area study of particles in the liquid phase, a straightforward titration is enough, although it need a so many work. Therefore, , or nuclear magnetic resonance spectroscopy, is employed. SMPS and the differential movement analyzer (DMA) are used to evaluate the surface area of nanoparticles in the gaseous phase.

-Concentration

The quantity of nanoparticle in the gaseous phase is monitored in order to calculate the amount of air or gas required for the operation. The performance or efficiency is shown by the size, distribution, and concentration of nanoparticles in one liter of gas or air. Condensation particle counters (CPCs) are typically used to measure concentrations.

-Composition

The purity and functionality of the nanoparticle are demonstrated by its chemical or elemental makeup. Higher levels of secondary or undesirable components in the nanoparticle can reduce its effectiveness and cause contamination and secondary reactions. The most common method for measuring composition is photoelectron spectroscopy with X-rays (XPS). Some methods, like spectrometry, atomic emission spectroscopy, and ion chromatography, entail chemically digesting the particles before performing wet chemical analysis. The particles in the gaseous phase are gathered either electrostatically or by filtering, and the analysis is done using wet chemical or spectrometric methods.

-Surface characteristics

In order to fully utilize its properties, the nanoparticle's many surface structures and forms are essential. Some of the shapes are spherical, slender, cylindrical, tubular, conical, and irregular, and their surfaces might be uniform or uneven, crystalline or amorphous. For surface determination, SEM /TEM are typically employed. While the particles in the gaseous phase are captured electrically or by filter for photographing using electron microscopy, the liquid phase particles are positioned on a surface and examined.

-Crystallography

The study of atom and molecular positions in crystal solids is known as crystallography. To ascertain the structural organization of nanoparticles, crystallography is carried out utilizing powder X-ray, electron, or neutron diffraction.

2) DRUG DELIVERY SYSTEM OF MATRIX TYPE

The advent of matrix tablets as sustained release (SR) has given pharmaceutical technology a novel idea for a ground-breaking drug delivery system. medication flow rate from the dosage form is primarily controlled by the kind and ratio of polymers used in the preparations, and it eliminates complicated production processes like coat and pelletization during manufacture. Formulating a sustained release dosage form primarily involves the use of a hydrophilic polymer matrix. The research and development of monitored drug delivery systems has received more attention as a result of the growing challenges and expenses associated with selling novel therapeutic molecules. [68] The goal of continual release is the main reason for using matrix systems. It is a diffusion system that prolongs and regulates the drug's dissolved or dispersed release. Actually, a matrix is a well-combined mixture of one or more medications with a gelling agent, such as hydrophilic polymers. By using the sustained release approach, a therapeutically effective concentration may be achieved in the systemic circulation over a longer period of time, improving patient compliance. Intense research is now focused on the development of prolonged release methods for poorly water soluble pharmaceuticals.

5.1 Matrix tablet benefits:

- Simple to create, practical, efficient, and reasonably priced
- High molecular weight chemicals can be released by formulation.
- The medicines with sustained release have the potential to regulate therapeutic concentrations over extended periods of time.
- High blood concentration is inhibited by the use or sustain release formulations.
- Formulations with sustained release have the potential to improve patient acceptability.

Reduce the toxicity by delaying the absorption of the medication.

- By protecting the medication against hydrolysis or other derivatives that alter in the gastrointestinal system, you can increase its stability.
- Minimizes both systemic and local side effects.

- Enhanced effectiveness of therapy.
- Overcoming drug buildup with long-term dosage.
- Enhance the bioavailability of a number of medications

5.2 Matrix tablet drawbacks:

After the medication is released, the leftover matrix has to be withdrawn.
High preparatory costs are necessary.
Various factors, such as the meal and the rate of transit through the stomach, affect the release rates.
The square root for time affects the medication release rates. A decrease in the area of effect at a diffusion front and/or an increase in diffusional resistance cause the release rate to steadily drop. However, extremely gradual release rates, which are undetectable from zero-order in many applications, can be used to provide a significant prolonged impact.

5.3 MATRIX TABLETS' ROLE

Creating a safe and efficient medication method of administration is one of the pharmaceutical industry's biggest difficulties. Therefore, it is necessary to maximize both the drug's properties and the way it is administered. Grid tablets are a crucial component of oral medications for the regulated and prolonged release of medication. To extend and maintain the rate of medication release, the tablet matrix is made using hydrophilic polymeric and hydrophobic lipids. The creation of matrix sustained formulations, including hydrogel-containing matrix tablets, is receiving a lot of interest these days. Because of their chemical inertness, affordability, regulatory acceptability, and adaptability in achieving the required drug release profile, matrix systems containing hydrophobic lipids have also been widely utilized in tightly controlled drug delivery applications. More focus has been placed on the creation of modified release systems for drug delivery as a result of the growing challenges and costs associated with selling novel medication compounds. For a certain amount of time, the controlled-release matrix system delivers the medication either systemically or locally at a predefined pace. More focus has been placed on the creation of delayed release drug delivery systems as a result of the growing challenges and costs associated with selling novel medication compounds. For a certain amount of a period of time a controlled release matrices system delivers the medication either internally or externally at a predefined pace. [71] One of the main ways that drugs are released from hydrophilic matrices is when the polymer swells upon coming into contact with an aqueous medium, creating a gel layer on the system's surface. The medication is then administered by erosion, diffusion, or dissolving. Over the past 20 years, further data was gathered to examine the advancements in the area of matrix tablet research.

5.4 The categorization of matrix tabulation

- Depending on the Retardant Material Employed:
- Matrices of Lipids
- Plastic matrices that are hydrophobic
- Matrices That Are Hydrophilic
- A Derivatives of cellulose:
- B. Natural or semi-synthetic polymers that are not cellulose:
- Matrix Biodegradability:
- Matrices of Minerals
- Matrix structures of fat-wax

-Three types of matrix tablets may be distinguished based on the matrix's porosity.

- Systems with macropores
- Microporous structure
- A system that is not permeable

5.5 DRUG RELEASE MECHANISM FROM the matrix TABLET:

- **The diffusion approach**

The drug spreads out of the matrix after initially dispersing in the outer layer that is exposed to the bathing solution. As the solid medicine moves toward the inside, an interface is formed between it and the bathing fluid. When using this procedure, the rate at which the drug particles dissolve inside the matrix of molecules must be significantly quicker than the rate at which the dissolved drug diffuses out of the matrix.
The following requirements must be met in order to derive the mathematical model that explains this system.
The drug release process is managed to create a pseudo-steady state.
b) The mean distance for drug diffusion through the matrix is greater than the diameter for the drug particles.

c) Sink conditions are always provided by the bathing solution. The following formula provides a mathematical explanation of the system's release behavior:

dM/dh = Co. dh - Cs/2 …… (1)

Where,

dM = Variation in the quantity of medication discharged per unit area

dh = Modification in the amount of thickness of the drug-depleted matrix zone

Co is the total quantity of medication in a matrix volume.

Cs is the drug's saturated concentration in the matrix.

Additionally, according to diffusion theory:

dM = (Dm. Cs / h) dt..... (2)

Where,

Dm is the matrix's diffusion coefficient.
h = Drug-depleted matrix thickness
dt = Time Change

By combining equation 1 and equation 2 and integrating:

M = [Cs. Dm (2Co −Cs) t] ½ …… (3)

When the amount of drug is in excess of the saturation concentration then:

M = [2Cs.Dm.Co.t] 1/2 …… (4)

The quantity of drug release is compared to the square root of time in equations 3 and 4. Plotting the drug release against the product of the square root time should thus provide a straight line if the system is mostly diffusion regulated. The synchronous penetration of the surrounding liquid, the drug's disintegration, and its leaching out through convoluted intermediate channels and pores constitute the release of medicine from a porous homogenous matrix.

5.6 MATRIX TABLET PREPARATION METHOD

A. Method of Wet Granulation [83]

- Drug, polymer, and excipients are milled and mixed.
- Making the binder solution.
- Wet massing through the addition of granulating solvent or binder solution.
- Inspection of the moist material.
- The wet grains are dried.
- Dry grains are screened.
- Compressing the pill after mixing with lubrication and disintegrant to create "running powder"

B. Method of Dry Granulation
-Drug, polymer, and excipients are milled and mixed.
-Slugs and compact powder are milled and screened after compressing into slugs --and roll compression.
-Mixing with disintegrant and lubricant
-Compaction of tablet

C. Method of Sintering
Sintering is the process of using heat to fuse the surfaces of neighboring particles in a compact or bulk of powder. The conventional sintering method involves heating a compact in a controlled environment to a temperature lower than the point of melting of the solid components. Sintering was cited as the cause of the changes in hardness and disintegrating time of tablets stored at higher

temperatures. The sintering procedure is used to stabilize and delay the release of the medicament as well as to fabricate sustained release matrix tablets.

5.6.1 Wet granulation technique

This technique uses a non-toxic granulating fluid, such as water, isopropanol, or ethanol (or mixes of these), to grow the size of tiny powder particles that agglomerate or join together form larger, stronger, and more fixed structures known as granules. The granulation fluid can be used as a solvent with a binder or granulating agent, or it can be used alone. The characteristics of the substances that need to be crushed play a major role in the choice of granulating fluid. The cohesive qualities of the granulating reagent should be conjugated with the formation of granules by powder mixing.

The degree to which the particles of powder combine to create aggregates (granules) determines the final product's characteristics and performance.

-Procedures for the Wet Granulation Method

Step 1: Measuring and combining the ingredients for the formulation.

In this phase, the necessary amounts of the drug substance or substances are weighed, sieved, and added to a powder mixer along with other ingredients such a disintegrant, filler, or diluent, and bulking agent. A planetary bowl mixer, ribbon/trough mixers, rotating drum mixers, or high-speed mixers are used to combine these additions until a consistent powder mixture is achieved. Although this is usually not the case for numerous mixing procedures, using powders with the same typical particle size might boost the mixing efficiency. Diluents used in the wet granulation process include the lactose , starch, granular sucrose, a substance called fructose/mannitol sorbitol, calcium phosphate, and calcium sulphate, while there are more diluents available on the market. Due to its low cost, solubility, and compatibility with the majority of medicinal compounds and excipients, lactose is the most often used diluent among all of these. Microcrystalline cellulose, due to its similar homogeneity of supply, ease of compaction, and compatibility with the majority of formulation components. The selection of diluents is often based on the manufacturer's familiarity with the substance, its cost, and how well it works with the medication and other additives. Disintegrants that counteract the effects of binders and the physical compression forces used to form the tablets include croscarmellose, salt /sodium starch glycolate, sodium carboxymethylcellulose, polyvinyl (PVP)pyrolidine, a substance called crospovidone, cations exchange resins, corn and potato starches, alginic acid, and other substances used in the wet granulation process. starch of sodium glycolate (5 percent of ration) & cros-carmellose (2percent of ratio are commonly utilized due to their rapid action and high water absorption.

- **Getting the wet mass ready**

By combining the binder solution with the granulated powder combination of excipients, an adhesive material can be created. The operator's competence determines how much binding medium and fluid are needed to create a moist and cohesive mass, but the final binder-powder combination ought to expand when pressed in the hand. Soft pills, capping, and poor adherence are the results of using too little binder. Hard tablets with delayed disintegration properties are produced using an additional binder solution. Aqueous preparations of cornstarch as molasses in methylcellulose, carboxymethylcellulose, Granulating agents include povidone solutions, glucose solutions, & solutions of MCC . Dry bindings / nonaqueous solvents can be utilized for pharmaceutical substances that are adversely affected by aqueous solutions.To create a granularity with an extra characteristic, flavorings or colorants might be used with the binding agent.

- **Wet screening**

Wet screening is the process of separating the moist powder into granules or pellets.

The wet substance powder combination is filtered through a screen with a mesh size of 6 to 12 in order to prepare wet granules. This can be done manually or with the use of appropriate equipment that extrudes the granules via holes in the device. After being made, the granules are equally distributed on trays and baked to dryness.

- **Moist granules drying**

In order to achieve a consistent weight or even moisture content, the screened damp granule are then dried using an oven at a regulated temperature of no more than 55C. The kind of active component and the amount of moisture required for the proper formulation of acceptable tablets determine the degree of humidity and drying time. For this purpose, fluidized-bed driers and shelf or tray driers can be employed.

- **Using dry screening to size the granulation**

A smaller screen than the one used to make the moist granules is employed to filter the dry granules. The ultimate tablet size is determined by the measurement of the punches, which in turn determines the length of the final grains. For this, screens with a mesh size of 14–20 are frequently utilized.

- **Oiling/Lubrication of granules**

Following dry screening, the screened and dried granules are shaken on a 250 mesh sieve to separate them into coarser and fine granules. Lubricant in a specified amount is run through a 200-mesh sieve. This lubricant is combined with the small particles prior to the incorporation of the coarse granules. Although the amount of lubricant utilized varies from formulation scientist to formulation scientist, it typically falls between 0.1% and 5% of the granulation's weight. Examples of lubricants that are frequently used in wet granulation include talc, starch, hydrogenated vegetable oil, magnesium and calcium stearates, stearic acid, and wax. It's important to note that disintegrant can be applied in either the initial stage (intragranular) or step 6 (extragranular), and occasionally in both the first and the sixth processes. Since the extragranularly included portion immediately breaks the tablet into the final compressed granules and the intragranularly added portion further erodes granules back to the initial powder particles, intragranular-extragranular incorporation seems to be the best incorporation method.

- **Granules being compressed into tablets**

In this phase, single unit punching or multi-station tablet press with the appropriate dies and punches compresses the combined grains. In order to enhance the uncoated tablets' aesthetic appeal, modify or control the release of medicinal substances from tablets,or cover the flavor of unpleasant medications, Compressed tablets might be covered. This is achieved by the use of coating solutions. to enclose or shield the core tablets or granules.

5.6.2 Dry Granulation Method

-sThe dry granulation techniques

Granules are typically prepared utilizing the dry granulation method by roller compaction or the slugging technique. Although the two methods are identical, they may provide different outcomes.

a) Slugging methodology

b) Compaction by rollers

5.7 USE OF NANOPARTICLES

a) Cancer treatment

Many patients' lives have been spared by the sort of therapy used to treat cancer today, but because the chemotherapeutic drugs are non-specific, the negative consequences of the treatment are severe and impact the entire body. The creation of nanoparticles opens up new possibilities for chemotherapy. Targeted medication administration at the cancer site or to a specific cell population using cleverly designed nanoparticles significantly reduces the harmful effects on other healthy tissues and organs. A few systems have been tested to provide this kind of treatment.

b) Testing for diagnosis

The shortcomings of fluorescent markers, such as color matching, fading of light after a single usage, and limited dye use due to bleeding impact, are impeding the application of the most recent diagnostic testing technologies. Researchers can reduce these drawbacks with the use of fluorescent nanoparticles.

Recently, there has been a lot of interest in theranostic nanoparticles, which are nanoparticles that may be utilized for both diagnosis and therapy. Numerous nanoparticle types, including as drug combines, dendrimers that surfactants aggregate (micelles and nanotubes), core-shell fragments, and carbon nanotubes, have used this tactic. It is feasible to control the route plus localization of these nanoparticles at the target location as well as the drug activity to evaluate treatment response by combining the drug and imaging agent in a single clever formulation.

c) Treatment for HIV and AIDS

Research suggests a way to increase the effectiveness of this treatment by creating polymeric nanoparticles that carry antiretroviral (ARV) medications both intracellularly and to the brain. HIV infections can also be prevented by combining this technique with vaccines.

Antiretroviral medication delivery and compliance have been greatly enhanced using nanotechnology. Antiretroviral medications must be able to pass through the mucosal epithelial barrier whether administered orally or through other non-parental methods (suppository, patches, etc.). Important locations for HIV infection and growth include lymphoid tissues. According to several publications, antiretroviral medication-loaded nanoparticles were able to hit macrophages and monocytes in vitro.

d) Delivery of nutraceuticals

The majority of nutraceuticals are lipophilic compounds, such as polyunsaturated lipids, various phytochemicals, and fat-soluble vitamins A, D, E, and K. Once more, nanotechnology provides a great deal of assistance, and the majority of research has focused on developing nanoparticle preparations that will enhance the dissolving processes of nutraceuticals. [108109,]

Curcumin (diferuloylmethane) is the most significant and researched of several nutraceuticals with anti-inflammatory in nature antioxidant activity, antiapoptotic, and antiangiogenic properties. Numerous methods, including liposomes as lipid vesicle and polymer-based nano-formulation, have been employed to address this issue because it is essentially water-insoluble and has extremely low bioavailability.

e) Sunscreens and Cosmetics

Long-term stability is a shortcoming of traditional UV protection sunscreens. There are several benefits to sunscreen that contains nanoparticles like titanium dioxide. Some sunscreens include titanium oxide & zinc oxide nanoparticles because of their ability to absorb and reflect UV radiation while remaining transparent to visible light. Iron oxide nanoparticles are used as a pigment in certain lipsticks.

f) Electronics

The use of nanotechnology in display technology is being encouraged by the increased need for large, brilliant screens in electronics, which are employed in televisions and computer monitors these days. Examples of tiny lead telluride, cadmium sulfide, and zinc selenide and sulfide are found in light-emitting diodes (LEDs) seen in contemporary displays. The need for a small, Improvements in portable consumer devices, such as laptops and mobile phones, have led to an increase in light and large-capacity batteries. Nanoparticles are the best material for batteries separator plates. Their frothy nature allows them to store a significant amount more energy than conventional batteries. Because of their enormous surface area, batteries built of tiny nickel and metallic hydrides require less recharging and have a longer lifespan.

g) The process of catalysis

Nanoparticles are more catalytically active due to their huge surface area. The nanoparticles are efficient catalysts due to their extremely large area to volume ratio. in chemical synthesis. One noteworthy use is the use of nanoparticles of platinum in car catalytic converters, which improve performance and drastically lower costs by lowering the quantity of platinum required due to the nanoparticles' extremely high surface area. In some chemical reactions, such as the transformation of nickel oxide into nickel , nanoparticles are used.

h) Drugs/Medicine

Through the use of nanotechnology in medication delivery, nanotechnology has advanced the medical industry. Drug delivery to certain cells is possible using nanoparticles. By retaining the medicine in the right place at the right dosage, the overall drug intake and adverse effects are especially reduced. This approach lowers the expense and adverse consequences. With the use of nanotechnology, damaged tissue may be replicated and repaired. Tissue engineering has the potential to replace conventional therapies like organ transplants and artificial implants. The development of carbon nanotube scaffolds for bones is one such instance. There are a few uses for gold in the Indian medicinal system known as Ayurveda. Using gold to improve memory is one such recommendation.

i) Food

Food By using nanotechnology, food production, processing, packaging, and protection are all improved. In the food packaging process, for instance, a nanocomposite coating can directly incorporate antimicrobial materials onto the surface of the coated sheet. As an illustration, the canola oil manufacturing sector uses nanodrops, a food ingredient intended to transmit vitamins and minerals.

j) Building construction

Nanotechnology speeds up, lowers the cost, and improves the safety of building operations. When a nanosilica (SiO_2) is mixed with regular concrete, for instance, the nanoparticles can increase the concrete's durability and mechanical qualities. The use of a form of ha (Fe_2O_3) nanoparticles increases the concrete's strength. Steel is a commonly utilized and readily accessible material in the building sector. utilizing nanotechnology in steel can improve its qualities; for instance, utilizing nanosize steel in bridge building results in stronger steel cables.

3) THE NEED OF WORK

Scientists have recently been inspired to create formulations using the nanoparticular technique, which offers a number of benefits, including a larger surface area that satisfies the Noyes-Whitney hypothesis of efficient drug absorption. Additionally, formulations with nanoparticles ranging in size from 10 to 1000 nm may improve the ability to dissolve, dissolving speed, permeability of the membrane, and bioavailability.

Utilizing nanoparticles because therapeutic & detecting agents, in addition to improving medication delivery, is crucial and urgent for a number of reasons. One of these is that conventional medications, which are now administered orally or via injection, are not necessarily produced with the best possible formulation for every item. A more creative kind of carrier system is needed for products that contain proteins and nucleic acids in order to increase their effectiveness and shield them from unintended breakdown. . It is noteworthy that particle size has a direct correlation with the effectiveness of the majority of medication delivery methods. Drug nanoparticles have increased solubility and, thus, improved bioavailability because of their tiny size and huge surface area. Second, the creation of novel medication delivery technologies is giving pharmaceutical companies an additional edge in expanding their business. Pharmaceutical firms are creating new formulations of their current medications due to innovative drug delivery. Patients will benefit from these novel formulations, but they will also generate a strong market force that will propel the creation of ever more potent delivery systems. Pharmaceutical corporations gain from this innovative technology since it offers fresh life to medications that were previously thought to be unmarketable due to their high toxicity and solubility.

4) Matrix Tablets' Function

One of the biggest problems facing the pharmaceutical business is creating a safe and effective medication delivery mechanism. Therefore, it is necessary to maximize both the drug's properties and the way it is administered. Matrix tabs are a crucial instrument for the regulated release of medication among oral medications. The creation of matrix formulations, such as hydrogel-containing matrix tablets, is now receiving a lot of interest. Because of their chemical inertness, affordability, regulatory acceptability, and adaptability in producing the intended drug release profile, matrix systems incorporating hydrophobic lipids have also been extensively utilized in controlled drug distribution applications. Poorly soluble medications have limited bioavailability and variable gastrointestinal absorption when taken orally. In order to improve oral bioavailability, a product's solubility or rate of dissolution may be improved in a variety of ways. Among them, reducing the native drug's particle size has drawn a lot of attention in the past ten years. Making particles that are in the nanometer category is a better technique to deal with the drug's bioavailability problems. Systems with nanoparticulate matrix may be regarded as potential vehicles for regulated medication administration. Candesartan is the medication candidate chosen for the trial. It is an antagonist of the angiotensin II receptor that is used to treat hypertension. One BCS Class II medication is candesartan. Because of their limited solubility and metabolic breakdown, these substances have low bioavailability. With a dosage of 16 mg, candesartan has an oral bioavailability of up to 15%. It has a 5–9 biological half-life.

5) AIM

- creation and assessment of Candesartan nanoparticulate matrix tablets utilizing various excipients and polymers.
- Hardness, which is drug-polymer interaction, invitro dissolution, weight fluctuation, drug content uniformity, and friability, and short-term stability were all evaluated for the manufactured matrix tablets.
- The goal is to increase the dosage form's bioavailability so that it can be released at the point of absorption.
- Preparing economical dosage forms in relation to marketed reference products.
- To get a stable formulation ready.
- To contain and regulate the drug's release using the formulation

6) PLAN OF WORK

- Drug Selection, Literature Review, Preformulation Study, and Bulk Drug Characterization
- Drug and excipient compatibility tests utilizing a Fourier Transformation Infrared Spectrophotometer
- Nanoparticle formulation, nanoparticle assessment, precompression matrix tablet evaluation, and nanoparticulate matrix tablets of candesartan formulation employing various polymers.
- Based on the in the laboratory release trials, the optimal batch of tablets is chosen.
- Tablets will be manufactured using the method of direct compression and assessed based on the composition of the chosen batch.
- Stability and FTIR analyses for the improved formulation.
- Assessment of the manufactured matrix tablet o Physical assessment o In vitro dissolution investigation

7) MATERIAL & EQUIPMENTS :

Table No 6.1 : List of Equipments Used

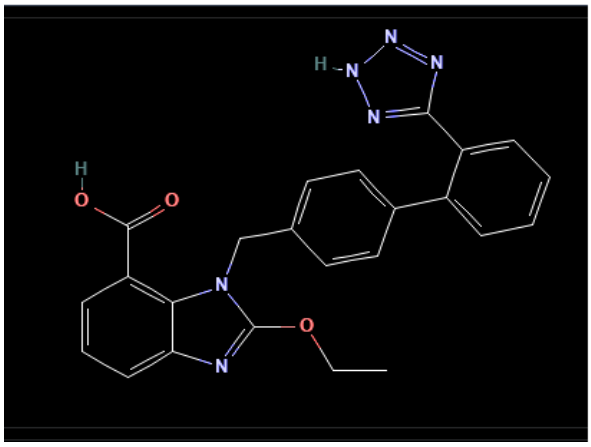
Sr. No.	Name of Chemical	Name of Supplier
1	Candesartan	Thermocil fine Chem Ltd. Pune
2	Eudragit RL 100	Thermocil fine Chem Ltd. Pune
3	Microcrystalline Cellulose	Thermocil fine Chem Ltd. Pune
4	Ethyl Cellulose	Thermocil fine Chem Ltd. Pune
5	Magnesium Stereate	Thermocil fine Chem Ltd. Pune
6	Talc	Thermocil fine Chem Ltd. Pune
7	Microcrystalline Cellulose	Thermocil fine Chem Ltd. Pune
8	Sodium dodecyl sulphate	Thermocil fine Chem Ltd. Pune
9	Ethanol	Thermocil fine Chem Ltd. Pune

Equipment's Used:

Table No 6.2 : List of Equipments Used

Sr. No.	Name of Equipment	Model /Company
1	Fourier Transform Infrared spectrophotometer	Bruker
2	UV-Visible spectrophotometer	UV 3200, Lab India
3	Electronic balance	Shimadzu
4	Multi tablet Punching machine	LAB PRESS, Cip Machinaries Ltd. Ahmedabad
5	Roche Friabilator	PSM Industries, Bangalore
6	Hot air Oven	Lab India
7	Hardness tester	Pfizer hardness tester
8	Dissolution test apparatus	DS-800, Lab India

8) DRUG PROFILE

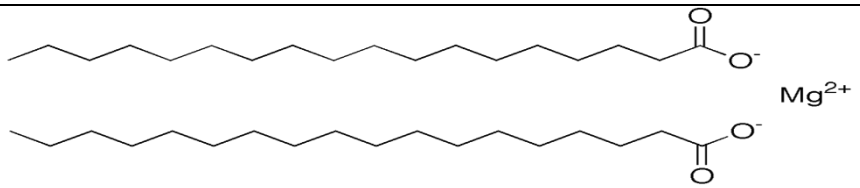
Sr. no	Name of Drug	Candesartan
1	**Structure**	
2	**Molecular Formula**	C24H20N6O3
3	**Molecular weight**	440.5g/mol
4	**Description**	Angiotensin II receptor antagonists like candesartan are used to treat hypertension. It affects the renin-angiotensin system in two ways. Vasodilation happens when vascular muscle mass relaxes and angiotensin II is unable to bind to AT1. The arterial pressure is further lowered by preventing the synthesis of norepinephrine.
5	**CAS number**	139481-59-7

6	**Indication**	The main reason candesartan is used is to treat hypertension, which lowers blood pressure and lowers the risk for cardiac events. Additionally, it is used to treat heart failure with a lower ejection fraction, alleviating symptoms and lowering hospitalization rates. Off-label usage for diabetes-related kidney disease is possible in some situations. By inhibiting angiotensin II receptors, the drug encourages vasodilation. .
7	**Pharmacodynamics**	By specifically blocking angiotensin II type I (AT1) receptors, candesartan inhibits the release of aldosterone and vasoconstriction. Blood vessel relaxation, a drop in blood pressure, and a reduction in cardiac workload result from this. Bradykinin metabolism is unaffected, which lowers the chance of coughing. It has a long-acting, dose-dependent antihypertensive impact. Because of its delayed, dissociative binding and high sensitivity for the receptor for AT1, candesartan provides a long-lasting antihypertensive impact. Without appreciably altering heart rate, it lowers blood pressure in both directions. After 4–6 weeks of consistent dose, the benefits reach their peak. The beginning of action is slow, usually occurring within 2 hours. Additionally, it reduces peripheral vascular resistance and plasma aldosterone levels. It lowers the risk of angioedema and dry cough since it doesn't build up bradykinin as ACE inhibitors do. .
8	**Mechanism of action**	Candesartan is a receptor blocker of angiotensin II (the ARB) that specifically prevents angiotensin II from attaching to the AT1 receptors in the adrenal glands and vascular smooth muscle. This results in vasodilation, decreased blood volume, and lowered blood pressure by blocking vasoconstriction and aldosterone secretion. Additionally, it reduces the heart's afterload and peripheral vascular resistance. It reduces the chance of cough and angioedema since it has no effect on bradykinin metabolism, unlike ACE inhibitors. Candesartan has a long-lasting antihypertensive impact by binding firmly to the AT1 receptor and dissociating gradually. In patients with heart failure, it improves cardiac output by lowering both preload and afterload. Over the course of 24 hours, the medication consistently lowers blood pressure and has no discernible agonist action.
9	**Absorption**	Candesartan is given as candesartan cilexetil, a prodrug that quickly transforms into the active medication in the gastrointestinal system after absorption. After taking 16 mg, its the oral absorption is around 15%. After injection, the highest plasma concentrations are obtained in three to four hours. Food barely affects how well it is absorbed. Its lengthy half-life guarantees efficient once-daily dosage even with limited bioavailability
10	**Metabolism**	Ester breakdown in the gastrointestinal system during absorption quickly and totally transforms the prodrug candesartan cilexetil into the active form, candesartan. The active form of candesartan is not significantly metabolized and only undergoes little hepatic metabolism, mostly via CYP2C9. It minimizes medication interactions by not inducing or inhibiting key cytochrome P450 enzymes. The majority of the medication is eliminated unaltered in bile and urine. Consistent therapeutic effects are supported by its predictable metabolism.
11	**Route of elimination**	With a binding efficiency of more than 99%, candesartan is

		widely attached to plasma proteins, primarily albumin. Its volume of dispersion is constrained by this strong protein binding. Even though it binds strongly, other medications do not substantially displace it.
12	**Protein binding**	With an adhesion rate of more than 99%, candesartan is widely attached to plasma proteins, primarily albumin. Its volume of dispersion is constrained by this strong protein binding. Even though it binds strongly, other medications do not substantially displace it.
13	**Half life**	oral administration is typically approximately 9 hours.
14	**Water Solubility**	Insoluble in water
15	**Log P**	4.7
16	**Melting point (°C)**	166-170 °C

9) EXCIPIENTS PROFILE

MAGNESIUM STEARATE

Content	**Description**
Name	Magnesium stearate
Non-proprietary Names	BP : Magnesium stearate Eur : Magnesium stearate US : Magnesium stearate
Synonyms	Magnesium octadecanoate; stearic acid magnesium salt; octadecanoic acid, magnesium salt.
CAS Number	[557-04-0]
Molecular formula	C36H70MgO4
Structure	
Molecular weight	591.34 g/mol
Category	Tablet & capsule lubricant.
Application	Mg stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0%. It is also used in barrier creams.
Description	Fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Properties	
Crystalline forms	High purity Mg. st. has been isolated as a trihydrate, a dihydrate and an anhydrate.
Bulk density	0.159 g/cm3
Flow ability	poorly flowing, cohesive powder.
Melting point	117-150oC (commercial samples)
	126-130oC (high purity Mg. stearate.)
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and H2O, slightly soluble in warm benzene and warm ethanol (95%).

Uses	Magnesium stearate is used as an anti-adherent. It has lubricating properties. It can also be used efficiently in dry coating processes. It acts as a release agent and it is used to bind sugar in hard candies such as mints. It is a common ingredient in baby formulas
Incompatibilities	Incompatible with strong acids, alkalis and iron salts, can't be used in products containing aspirin, some vitamins and most alkaloid salts.
Safety	Widely used as a pharmaceutical recipient and is generally regarded as being non-toxic following oral administration

MICROCRYSTALLINE CELLULOSE

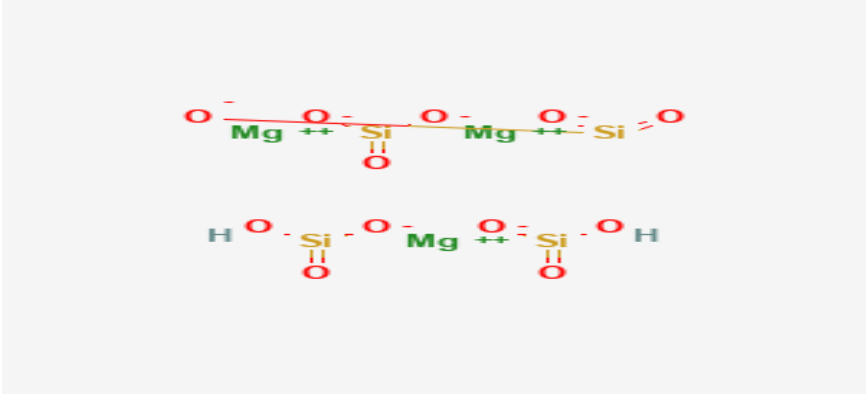
Content	Description
Name	Microcrystalline Cellulose
Non-proprietary Names	BP: Microcrystalline cellulose JP: Microcrystalline cellulose PhEur: Cellulose Microcrystallinum USP: Microcrystalline cellulose
Synonyms	Avicel; cellulose gel; crystalline cellulose; E460; Emcocel; Fibrocel; Tabulose; Vivacel
CAS Number	[9004–34–6]
Molecular formula	(C6H10O5)n
Molecular weight	36,000. Where n= 220
Category	Adsorbent; suspending agent, tablet and capsule diluent; tablet disintegrant.

Application	MCC 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 process. In addition to its use as a binder/ diluent, MCC also has some lubricant and disintegrant properties that make it useful in tabletting. Also used in cosmetics and food products.

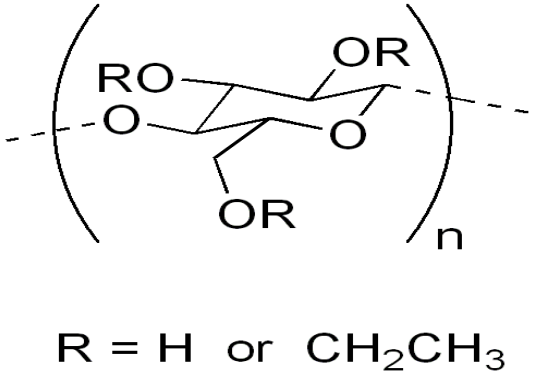
Description	MCC is purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades, which have different properties and applications.
Properties	
pH	5.0 - 7.0
Bulk density	0.32g/cm^3
Crystalline forms	Powder

Melting point	Chars at 260-270oC
Solubility	Practically insoluble in water, in acetone, in anhydrous ethanol, in toluene, in dilute acids and in a 50 g/L solution of sodium hydroxide
Storage conditions	MCC is a stable, though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.
Uses	Adsorbent 20-90 (%) Anti-adherent 5-20 (%) Capsule binder / diluents 20-90 (%) Tablet disintegrant 5-15 (%) Tablet binder / diluents 20-90(%)
Incompatibilities	Incompatible with strong oxidizing agents.
Safety	MCC is widely used in oral pharmaceutical formulations and food products and is generally regarded as a non-toxic and non- irritant material.

TALC

Content	**Description**
Name	Talc
Non-proprietary Names	BP: Purified talc JP: Talc USP: Talc
Synonyms	Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.
CAS Number	[14807-96-6]
Molecular formula	H2Mg3O12Si4
Structure	
Molecular weight	379.27 g/mol

Description	Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
	Properties
pH	7–10 for a 20% w/v aqueous dispersion.
Bulk density	2.58-3.83
Crystalline forms	Crystalline Powder
Moisture content	Talc absorbs insignificant amounts of water at 258C and relative humidities up to about 90%.
Refractive index	1.54–1.59
Solubility	Practically insoluble in dilute acids and alkalis, organic solvents, and water.
Storage conditions	Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.
Uses	Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.
Incompatibilities	Incompatible with quaternary ammonium compounds.
Safety	Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants. Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.
Category	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
Application	It is widely used as a dissolution retardant in the development of controlled-release products. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

Content	Description
Name	Ethyl Cellulose
Category	Coating and Flavoring agent, Tablet binder
IUPAC name	Cellulose ethyl ether
Synonym	Ethyl Ether; Ethylated Cellulos, Ethocel
CAS No.	9004-57-3
Structure	 $R = H \text{ or } CH_2CH_3$
Molecular formula	variable
Molecular weight	variable
Description	Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder

10) EXPERIMENT :

Technique and Experimental Work
Section I: Drug-loaded nanoparticle preparation and assessment

STUDIES BEFORE FORMULATION:
The initial stage in the logical creation of drug substance dosage forms is pre-formulation testing. The process of improving medication delivery by identifying the physicochemical characteristics of excipients that may impact drug performance and the creation of an effective, stable, and safe dosage form is known as pre-formulation studies. It offers a structure for the medication combination in the dose form with pharmaceutical excipients**.**

PHYSICAL ATTRIBUTES
Study of solubility :
Candesartan's solubility was investigated in five distinct volatile solvents: propylene glycol, glycerine, polysorbate 80, and PEG 400. Candesartan was added in excess to the carrier for 48 hours at 25 °C while being constantly stirred to create a saturated solution. Following this time frame, the solution was filtered, diluted at least 1000 times with distilled water, and examined using a UV spectrophotometer set to 258 nm.

Decrease in Drying :

dried for three hours at 100 degrees Celsius to 105°C in an oven to determine 1 gram. Combine the material to be tested and weigh it precisely. If the specimen is in a shape of big crystals, crush it quickly to decrease the particle diameter to roughly 2 mm. To be used in the determination, tare a shallow weighing container with a glass stopper that has been drying for thirty minutes beneath the same circumstances. After replacing the bottle's cover, insert the sample as precisely as possible down to a level of around 5 mm. The loaded bottle should be put inside the drying chamber. For a consistent weight, dry your specimen at the designated temperature. Before weighing, quickly seal the bottle after opening the chamber and let it reach ambient temperature in a desiccator. There should be a maximum of 0.5 milligrams between consecutive weights. The following formula is used to determine the drying loss:

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Where, W1 = Empty Weighing Bottle Weight W2 = Weight of sample plus weighing bottle
W3 is the weight of the dry sample plus the weighing bottle.

-CANDESARTAN STANDARD CURVE CONSTRUCTION

-Through the use of UV spectroscopy: Spectrophotometric estimation of candesartan is made at 258 nm.

Finding the maximum absorbance (λ max) :

Using the appropriate dilution, candesartan was dissolved in a pH 6.8 phosphate buffer solution at a concentration of 20 µg/ml. Using phosphate buffer pH 6.8 as a blank, the solution was scanned in a UV spectrophotometer between 200 and 400 nm. The highest absorbance was found to be 258 nm. The absorbance at 258 nm in phosphate buffer pH 6.8 was then used to quantify the medication.

Candesartan calibration curve: 10 mg of precisely weighed candesartan mesylate were dissolved in 1 ml of methanol in a 10 ml volumetric flask, & the remaining volume was filled with a buffered phosphate pH 6.8 to produce a stock solution with a 100 micro grams per milliliter concentration. To achieve different dilutions (10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 µg/ml) into standard volumetric containers (10 ml), the standard solution was diluted with a buffered phosphate solution PH 6.8. The 200–400 nm wavelength range was used to scan the dilution. At 258 nm, candesartan mesylate reached its maximum. A linear association was seen between 10 and 100 µg/ml. At 258 nm, absorbance was measured using Acidity 6.8 phosphate buffer to serve as blank. A calibration graph was created by plotting the drug's absorbance against its concentration.

- **PRE-FORMULATION STUDY**

- DRUG AND POLYMER COMPLIANCE STUDY BY FTIR In pharmaceutical formulation, compatibility is one of the requirements for choosing an appropriate excipient. Accordingly, to confirm any potential chemical interactions between the drug Candesartan and the polymer Eudragit RL 100, a study was conducted using a Fourier transformed infrared (FT-IR imaging) spectrophotometer. The IR by potassium pellet method was conducted on pure substances, i.e., the drug Candesartan and the polymer Eudragit RL 100, separately as well as their physical mixture. A transparent pellet was formed by compressing under 15 tons of pressure in a hydraulic press, and the potassium pellet was scanned to 4000 to use a spectrophotometer at 400 cm-1. The spectral profile of the physical mixture has been contrasted to the initial spectra in order to detect any possible chemical interactions between the drug and polymer. The selective light absorption of the sample by the shaking modes of certain bonds of chemicals is quantified by analysis utilizing FTIR. By examining the sound /spectrum vibration of the medicinal product that is encapsulated, the kind of relationship that exists between the medication and the polymer is determined.

Table 9.1: Formulation of Nanoparticle

S.NO	ormulation code	Drug in mg	ymer Eudragit RL 100
1	F1	400	10
2	F2	400	20
3	F3	400	30
4	F4	400	40
5	F5	400	50
6	F6	400	60
7	F7	400	70
8	F8	400	80

A) METHOD FOR CANDESARTAN NANOPARTICLE PREPARATION

1) Method of Solvent Evaporation :

Every batch of nanoparticle are produced using the solvent evaporation process. First, fifty milligrams of the sodium dodecyl sulfate was mixed in 10 ml of water after the necessary amount of medicine and polymer had been thoroughly dissolved in Ten ml of ethanol. Next, a syringe was used to combine the medication and polymer combination with the sodium dodecyl sulfate solution. The mixture had been homogenized utilizing a vortex mixture for one minute, after which the item was sonicated in order to reduce its size.. Solvent was evaporated and nanoparticles collected using a flash evaporator.

B) Analyzing the particle size of nanoparticles and evaluating them

1) T.he Malvern size analyzer may be used to determine the size of the produced nanoparticles. The materials were dissolved in water and put in a sample unit (disposable sized cuvette) for this analytical technique. After that, we set our measurement location (mm) and put the cuvette in the analyzer. The analyzer may be might be used to ascertain the particles' average size of samples (diameter in the nanometric range) as well as the distribution of sample particle sizes. To find the size distribution, plot a graph of intensity (percent) against size (d.nm).

2)Determination of Surfaces Charge (ZETA Potential)

Potential zeta is a crucial metric for assessing and determining the ideal stability state for dispersed or colloidal systems. A a zeta potential analyser (Malvern Zeta Seizer) was used to characterize the produced nanoparticle suspension in terms of zeta potential. Zeta potential, which is an electrical charge on a particle's surface that forms an electrical barrier, which is essential for medication stability.It was investigated how Eudragit RL 100 affected the nanoparticle's surface characteristics.

3) A study on drug entrapment

The quantity of drug found in the transparent supernatant following centrifugation was measured (w) using a UV spectrophotometer set to 258 nm in order to determine the degree of drug entrapment.For this, a standard medication calibration curve was plotted. The total quantity of drug introduced during the preparation (W) was then deducted from the quantity of drug in the supernatant. Effectively, the amount of medication trapped in particles may be determined using (W-w).

The equation % Drug Trapping = (W-w devided by W) × 100 was then used to calculate the percentage entrapment of a drug.

The amount of free medication in the supernatant, which is produced after by centrifuging a solid lipid solution at Using the ultra centrifuge set at 15,000 revolutions per minute for twenty minutes at 0°C,was used to determine the efficiency study. The absorbance was determined using UV spectrophotometry at 258 nm.

Investigations of Intravenous Drug Release Using the UV Spectrophotometric Method :

The diffusion membrane method was used to conduct the in vitro drug release investigation. The preparation of the nanoparticles was put on a membrane for dialysis and poured into a beaker with 200 ml of diffusing medium (phosphate buffers saline 7.4). The medium was kept at 37 °C while being constantly stirred by a magnetic field. Every hour at a predetermined interval, 1 milliliter of the sample was removed from its diffusion medium and replaced with 1 milliliter of fresh media. This procedure was run for a whole day. At 258 nm, the sample was analyzed using UV spectrophotometry.

PART II

NANOPARTICULATE MATRIX TABLET FORMATION

Pre-formulation Research

Drug Excipient Analysis Using FTIR

A Thermo Nicolet FTIR was used for infrared spectroscopy, and the spectrum was captured between 4000 and 400 cm-1. By looking for any change in the drug's peaks in the spectrum of the physical combination of drugs, IR spectral investigations were able to determine the interaction between the drug and excipients. Method: A weighed dose of the medication (3 mg) was combined with 100 milligrams of potassium bromide, which was dried at 40–50 degrees Celsius. To create a translucent pellet, the mixture was squeezed in a press powered by hydraulics at a 10-ton pressure. An infrared spectrophotometer was used to scan the pellet. The same process is utilized for all pertinent excipients.

11)Nanoparticulate Matrix Tablet Preparation

Nanoparticulate matrix tablets are prepared using the direct compression process. By using the direct compression approach, candesartan as nanoparticulate matrix tablets have been developed. The matrix-like tablets were created by directly compressing them using a punching machine after the appropriate amount of medication and excipients had been precisely weighed and combined.

Table 9.2: Formulation of nanoparticulate matrix Tablet

Batch	F1	F2	F3	F4	F5	F6
Drug Loaded Nanoparticle	480	480	480	480	480	480
Microcrystalline Cellulose	16	14	12	--	--	--
Ethyl Cellulose				16	14	12
Magnesium Stearate	2	3	4	2	3	4
Talc	2	3	4	2	3	4
Total	500	500	500	500	500	500

Assessment of Matrix Tablets

-Assessment of Precompression

Using established techniques, the bulk density, tapping density, compression index, Hausner ratio, and flow characteristics (angle of repose) of mixed powder were assessed. Every study was conducted in triplicate (n = 3), and the corresponding standard deviation is included with the average data.

Tapped density and bulk density

The prepared granules' tap bulk density (TBD) and loose bulk densities (LBD) were both measured. A 50ml measuring cylinder was filled with 10 grams of each formula's mix, which had been shaken to break up any agglomerates that had formed. Using a bulk densitometer, the cylinder was permitted to drop 2.5 cm from its height onto a hard surface on its own weight in order to measure the original volume. The tapping was kept up until there was no more audible variation. The following formulas were used to determine LBD and TBD. As per the USP-NF Guidelines, a sample weighing 100 grams was collected. The quantity of the specimen to be tested and the cylinder's volume may be changed if 100 grams cannot be used.

LBD : is the total weight for the granules divided by the packing's untapped volume.

TBD : Granule weight divided by the packing's tappled volume is TBD.

Index of Compressibility

Carr's compressibility index was used to calculate the blend's index. It is a straightforward test to determine a powder's LBD and TBD as well as its packing down rate.

The following is the formula for Carr's Index:

Carr's Index: (TBD-LBD) x 100 = Carr's Index (%)/TB

The Hauser Ratio

The following equation was used to get Hauser's Ratio.

Hauser's Ratio= Tapped Density / Bulk Density

Angle of repose

The height and diameter of the granule pile were measured in order to calculate the angle of repose. The bottom of a funnel that was attached to a stand was three centimeters above the plane. The height and diameter of the granule pile were measured after the granules were put in a funnel and let to flow freely. After adding lubricants and glidants that were computed using the equation, similar investigations were conducted.tan $\theta = h/r$

where h and r stand for the powder cone's height and radius, respectively.

Evaluation Following Compression

Test of hardness

It shows how resistant a tablet is to handling-related mechanical shocks. A verified Monsanto hardness tester was used to measure the tablets' hardness. The unit of measurement is kg/cm^3.

From each batch, six tablets were chosen at random in accordance with USP Guidelines, and their hardness was assessed.

Tablet's thickness

For tablets to be the same size, their thickness is crucial. Vernier Callipers were used to measure thickness. Ten tablets from each formulation batch were measured for thickness in order to make this determination.

Test of weight variation

To guarantee that each tablet contains the right amount of medication, the total weight of the tablets being manufactured was regularly measured. To perform the USP variation in weight test, 20 tablets are weighed separately, the average weight is determined, and the individual weights are compared to the average. The tablets satisfied the USP requirement that no tablet deviates from the % limit by more than two times, and that no tablet is beyond the limits by more than two.

Test of Friability

The friability test was conducted using the Roche friabilator. Twenty pre-weighed tablets (W Initial) were put in the friabilator equipment and spun for four minutes at 25 rpm in accordance with IP recommendations. Tablets were weighed once more (Wfinal), and the following formula was used to calculate the percentage weight reduction in each tablet:

$$\% \text{ (per.)Friability} = \frac{\text{initial mass/wright of the tablets} - \text{final mass/weight of the tablets}}{\text{the tablets' initial weight}} \times 100$$

Content of Drugs

Each batch of ten pills was weighed, and the average weight was determined. 400 mg of the medication was dissolved in 100 milliliters of phosphate buffer 6.8 after all of the pills had been crushed and ground into powder. One milliliter of the stock solution was transferred into a ten milliliter volumetric flask, and the amount present was reduced using phosphate buffers with a pH of 6.8. After filtering the solution, the absorbance at 258 nm was determined using spectrophotometry with a blank of pH 6.8 phosphate buffer. The amount of medication contained in a single pill was determined.

Studies on in vitro dissolution

At 50 rpm, the USP-II (Paddle) dissolving equipment was used to conduct the in-vitro dissolution experiments. Temperature continued at 37±0.50C, and the dissolution medium was 0.1 N hydrogen chloride for the first two hours and a buffer with phosphate pH 6.8 for the remaining hours. At certain intervals, 5 ml of the media was removed, and the same volume of new medium was added. Using the pH 6.8 solution as a blank, the extracted materials were diluted with it, filtered, and then examined use a UV spectrophotometer at 258 nm. The proportion of cumulative drug release was calculated.

Dissolution Parameters

Equipment for dissolution tests: Type II USP

50 rpm is the speed.

Stirrer type: paddle

Medium volume: 900 milliliters

Withdrawn volume: 5 ml

Phosphate buffer 6.8 was the medium.

Climate: 37±0.5ºC

Drug release profile modeling using mathematics

By examining the release data using zero order, the first-order kinetics, and the Higuchi equation, the drug releasing from the Candesartan was sustain releasing matrix tablets was investigated. By fitting the information to Korsmeyer Peppas' model, the release process was comprehended.

Zero order kinetics

A linear plot of cumulative percentage drug release vs time indicates that the data follows zero-order release kinetics, having a slope of K0. The following formula would anticipate a zero order release:Where At = the release of drug at time "t,"

At = A0-K0t.

A0 is the initial concentration of the medication. K0 is equal to the zero-order rate constant (hr-1)

Kinetics of the first order

Plotting the data by log total percentage of medicine left vs. time yields a straight line, indicating that the release corresponds to first order kinetics. The constant K may be obtained by multiplying the slope values by 2.303.

The following formula would anticipate a first-order release:Log C is equal to log C0 minus Kt / 2.303.

where C is the amount of medication that was left at time t.

C0 is the drug's initial concentration.

K is the rate constant of the first order (hr-1).

The Higuchi model

A straight line is produced when the data is shown as cumulative release of drugs against a square root over time, suggesting that the medication was released by a diffusion mechanism.

Q = [Dε / ε (2A - εCS) CSt]1/2

where Q is the quantity of medication released at time t.

D is the drug's diffusion coefficient within the matrix.

A = Total drug content per matrix volume.

CS stands for drug solubility in the matrix.

ε = The matrix's porosity.

Tortuosity is equal to t.

Peppa's model/Korsmeyer equation

A straight line having a slope of n is produced when information is plotted as the logs of drug released vs time, and the y-intercept may be used to determine the K. The well-known exponential equation, also known as the Korsmeyer equation or Peppa's law equation, which is frequently used to characterize the way drugs release from polymeric materials, was also fitted to the release data in order to investigate the mechanism of drug release.

where the proportion of medication released at time (t) is represented by Mt / Ma.

K = Constant that takes into account the drug's or polymer's geometrical and structural properties.

n = Diffusion factor associated with the release method.

By using log on both sides, the above equation may be made simpler: Log Mt / Ma = Log K + n log t

For Fickian release, n = 0.5, but for anomaly (non-Fickian) transport, n ranges from 0.5 to 1.0.Studies of stability

The ICH (Q1A (R2), 2003) criteria were followed for conducting stability studies. Optimized matrix tablets were subjected to three months of long-term stability in stability chambers (Thermo lab, Mumbai, India) at temperatures and relative humidity (RH) levels of 250 C and 60% RH.

12) RESULT AND DISCUSSION :

Appearance of Nano Particle:

Drug Candesartan and Eudragit RL 100 complex nanoparticle have been prepared as per given procedure and found stable with following appearance.

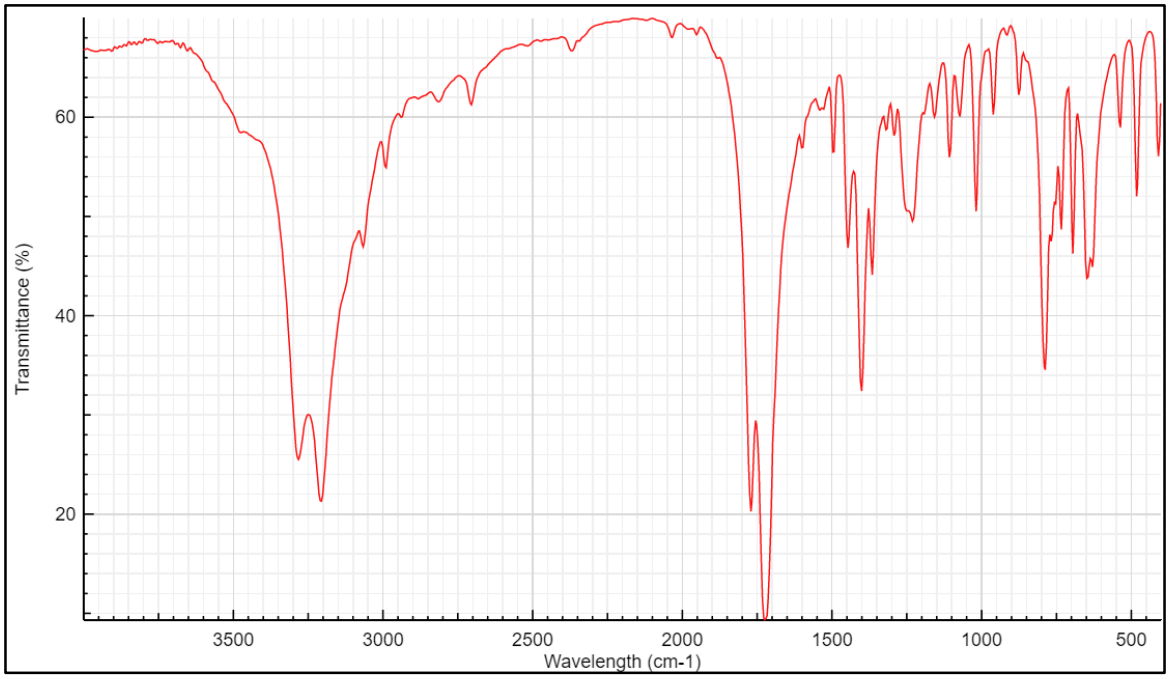
Table 9: Physical Appearance of Nanoparticle

Parameter	Candesartan and Eudragit RL 100 complex nanoparticle
Appearance	Clear particles observed
Nature	Fluffy in nature

Synthesis of drug polymer nanoparticles was carried out by using solvent evaporation method. It was performed in two steps; first step was wet impegration method and second step was dry reduction reaction. Formation was confirmed by following techniques:

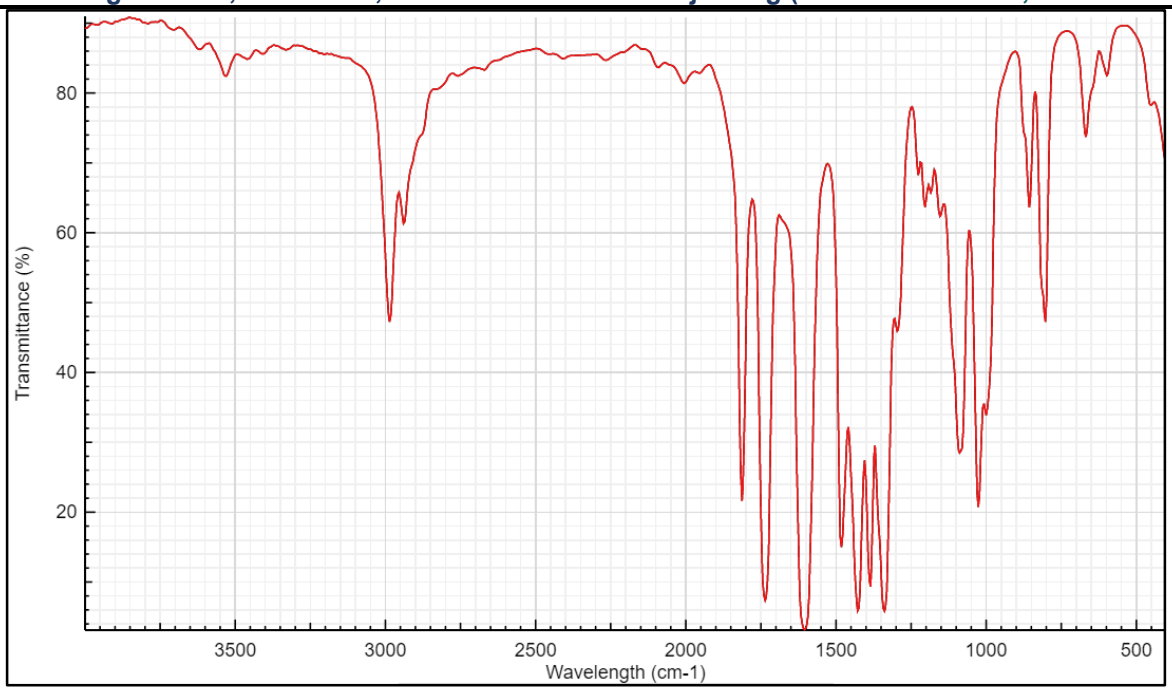
- IR analysis
- XRD analysis
- SEM analysis
- EDS analysis

1. FTIR analysis:



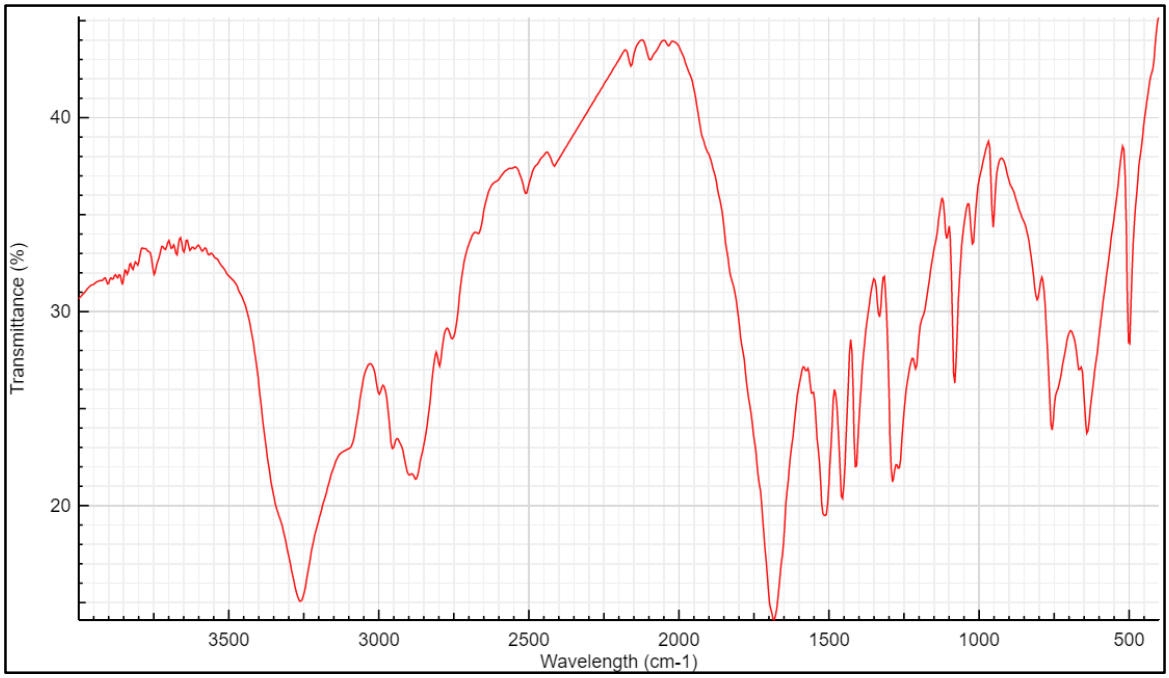
Spectrum 1 : IR of Candesartan

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretch	3471
2	-OH stretch	3234
3	=C-H Aromatic stretch	3041
4	=C-H Stretching	2962 2934 2876
5	-C=O stretching Conjugated vinyl bond	1706
6	-C-S linkage stretching	772



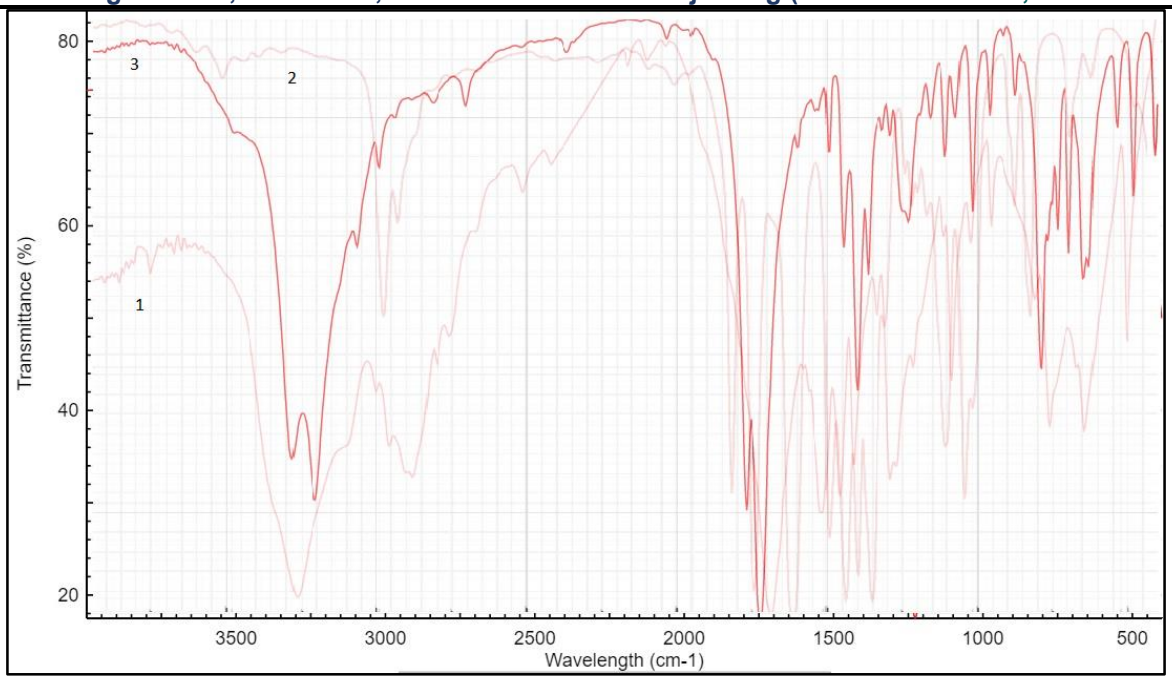
Spectrum 2 : IR of Eudragit RL 100

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretch	3039
2	-C=O stretching Carboxylic carbonyl group	1735
3	-C=C stretching	1476
4	-C-O stretching	1266 1164



Spectrum 3 : IR of Candesartan + Eudragit RL 100 Nanoparticle

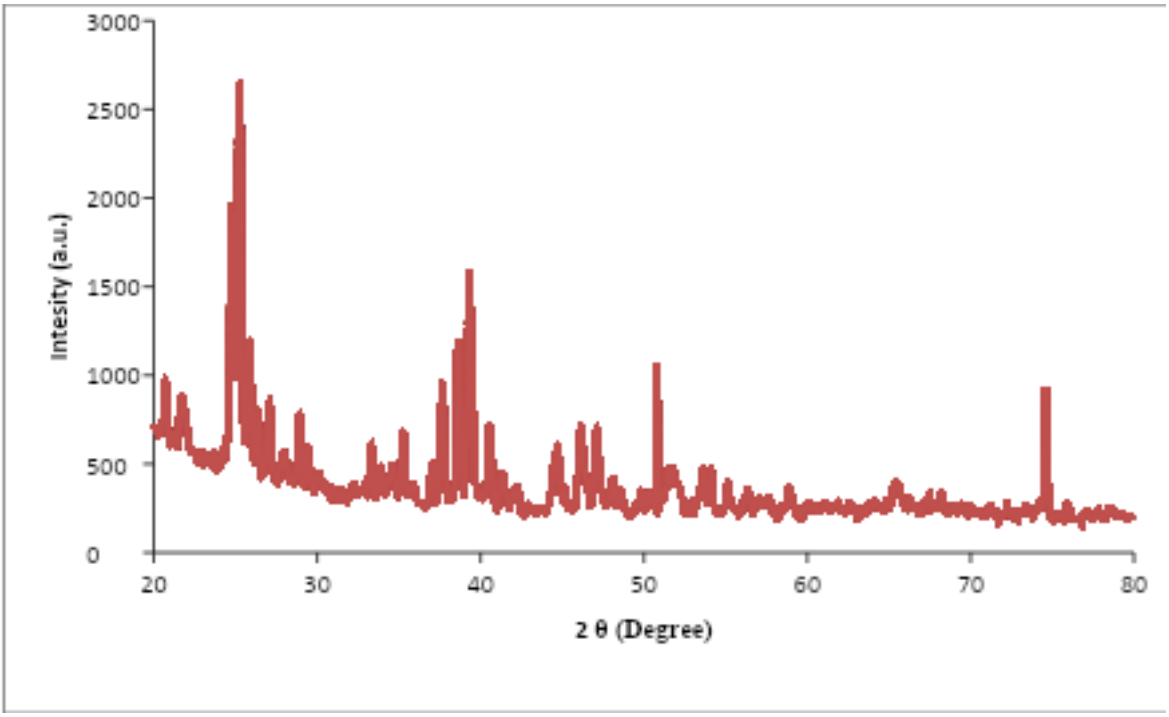
In FTIR spectrum of nanoparticle, broad merge peak of 3471 & 3039 cm^{-1}-OH stretching has been appear at around 3400 cm^{-1}. -C-H stretching appeared more distinct and carbonyl peaks appeared sharper in fingerprint area.



Spectrum 3 : IR of spectrum of Overlay

Note: In overlay No 1 is spectrum of Drug with Eudragit RL 100 and No.2 and 3 are Eudragit and drug respectively.

2. XRD analysis: XRD spectra help to confirm formation of nanoparticles and also presence of drug is confirmed from large peak between ranges of 2θ of 20-30.



Spectrum 2: XRD pattern of Candesartan + Eudragit RL 200 nanoparticles

XRD spectrum shows four larger peaks at 2 θ values of 39.3, 50.08 and 74.6 deg which are corresponding to planes of copper whereas peak at 25.2 deg is due to presence of Candesartan in nano powder.

The average particle size of nanoparticle was found from Powder XRD pattern by using Debye-Scherrer's formula:

$$D = \frac{0.9\,\lambda}{\beta \cos\theta}$$

$$\beta = \frac{(2\theta \text{ high} - 2\theta \text{ low})\ 3.14}{180}$$

Where,

0.9 is Shape factor and λ is X-ray wavelength, (λ = 0.1540 nm)

θ is Differaction angle.

β is Full width at half maximum (FWHM) of diffraction peak

Calculations of particle size:

1. $2\theta = 25.2^0$

$\beta = (25.3^0 - 25.1^0) \times 3.14 / 180$

$\beta = 0.0034$ radians

$$D = \frac{0.9 \times 0.1541}{0.0034 \times \cos(12.6)} = \mathbf{41.81nm}$$

2. $2\theta = 39.3^0$

$\beta = (39.5^0 - 39.2^0) \times 3.14 / 180$

$\beta = 0.0052$ radians

$$D = \frac{0.9 \times 0.1541}{0.0052 \times \cos(19.6)} = \mathbf{36.31nm}$$

3. $2\theta = 50.8^0$

$\beta = (50.9^0 - 50.7^0) \times 3.14 / 180$

$\beta = 0.0034$ radians

$$D = \frac{0.9 \times 0.1541}{0.0034 \times \cos(25.4)} = \mathbf{43.12nm}$$

4. $2\theta = 74.6^0$

$\beta = (74.8^0 - 74.4^0) \times 3.14 / 180$

$\beta = 0.0069$ radians

$$D = \frac{0.9 \times 0.1541}{0.0069 \times \cos(37.3)} = \mathbf{21.73nm}$$

Calculations of d-Spacing:

The value of d (the interplanar spacing between the atoms) is calculated using

Bragg's Law: $2d\sin\theta = n\lambda$

$$d = \frac{\lambda}{2\sin\theta} (n = 1)$$

1. $2\theta = 25.2^0$

$\theta = 12.6^0$

$$d = \frac{0.1541}{2 \times \sin(12.6)} = \mathbf{2.29nm}$$

2. $2\theta = 39.3^0$

$\theta = 19.6^0$

$$d = \frac{0.1541}{2 \times \sin(19.6)} = \mathbf{0.113nm}$$

3. $2\theta = 50.8^0$

$\theta = 25.4^0$

$$d = \frac{0.1541}{2 \times \sin(25.4)} = \mathbf{0.291nm}$$

4. $2\theta = 74.6^0$

$\theta = 37.3^0$

$$d = \frac{0.1541}{2 \times \sin(37.3)} = \mathbf{0.198nm}$$

Table 10: Particle size determination of Candesartan + Eudragit RL 100 nanoparticles

2θ of the intense peak (deg)	θ of the intense peak (deg)	FWHM of intense peak (β) radians	Size of particle (D) nm	d-spacing nm
25.2	12.6	0.0034	41.81	2.29
39.3	19.6	0.0052	36.31	0.113
50.8	25.4	0.0034	43.12	0.291
74.6	37.3	0.0069	21.73	0.198

3. SEM analysis:

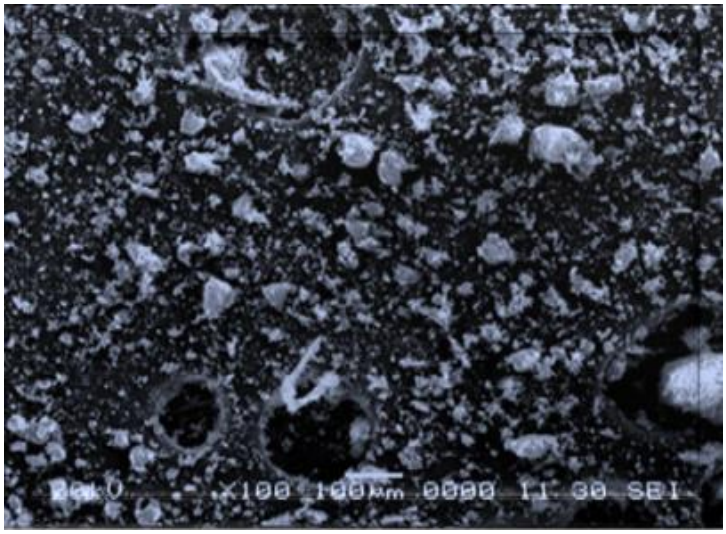


Figure 2: SEM image of Candesartan + Eudragit RL 200 nanoparticles

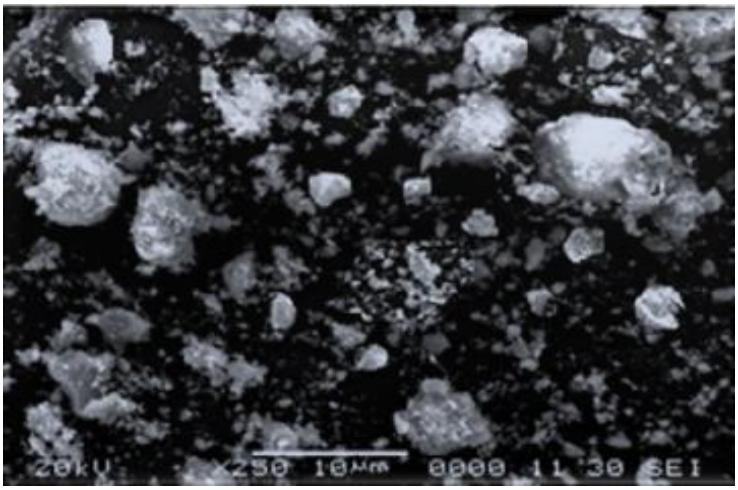


Figure 3: SEM image of nanoparticles showing deposition of Candesartan on Eudragit RL100 Support

Candesartan + Eudragit RL 200 nanoparticles have been characterized by SEM, in order to observe morphology of nanoparticles. Scanning done for size 10 to 100 µm.

4. EDS analysis: This analysis help to understand elements of Candesartan + Eudragit RL 200 nanoparticles like presence of Candesartan, Eudragit RL 100 and Oxygen from their energy dispersion.

Table 11: Acquisition Parameters of **Energy Dispersive Spectrometer**

Instrument	6360(LA)
Acc. Voltage	20.0 kV
Probe Current	1.0nA
PHA mode	T3
Real Time	70.37 sec
Live Time	30.00 sec
Dead Time	57 %
Counting Rate	17175 cps
Energy Range	0 - 20 keV

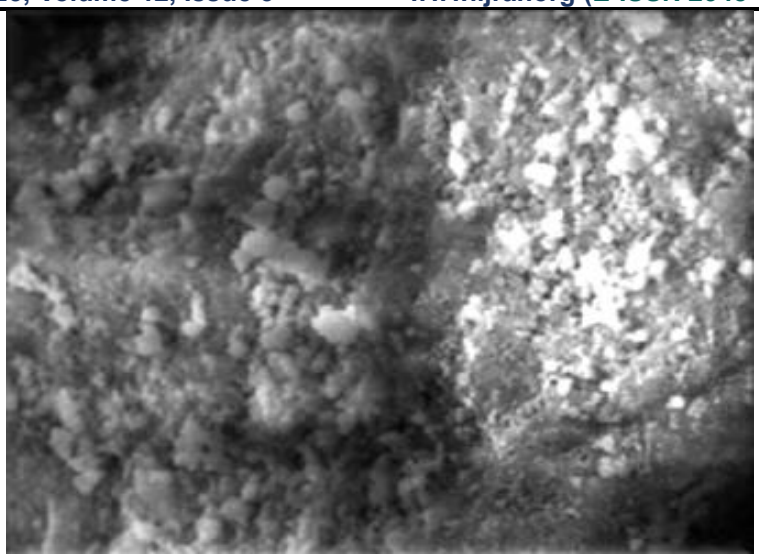
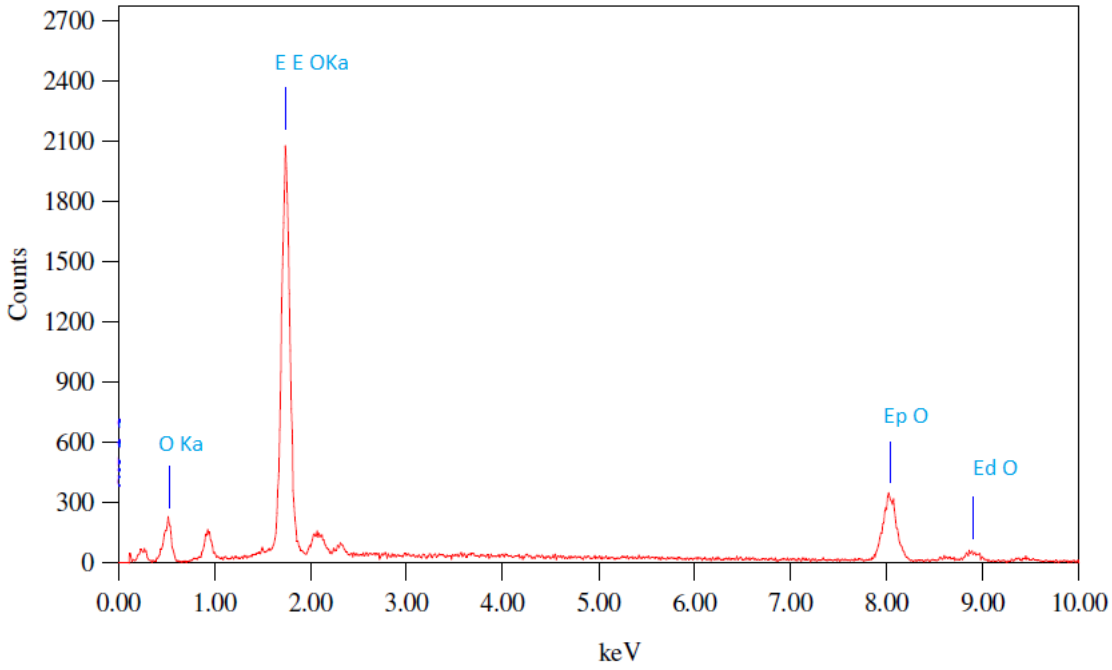


Figure 4: Nanoparticles surface used for EDS analysis



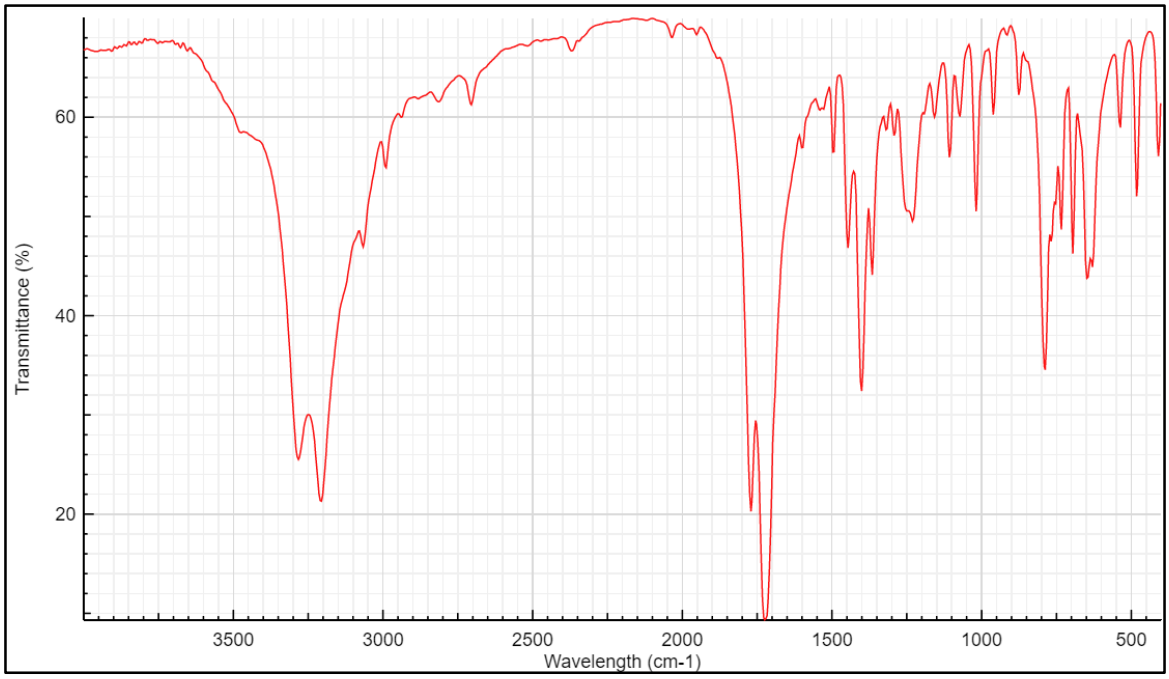
Spectrum 3: EDS analysis of Eudragit Supported nanoparticle

ZAF Method (Standard less Quantitative Analysis) was used for EDS analysis of Eudragit Supported nanoparticles with Fitting Coefficient: 0.473. EDS analysis help to understand Elemental composition of material by giving information about Energy dispersed by each element present in material.

Table 12: Results of EDS analysis

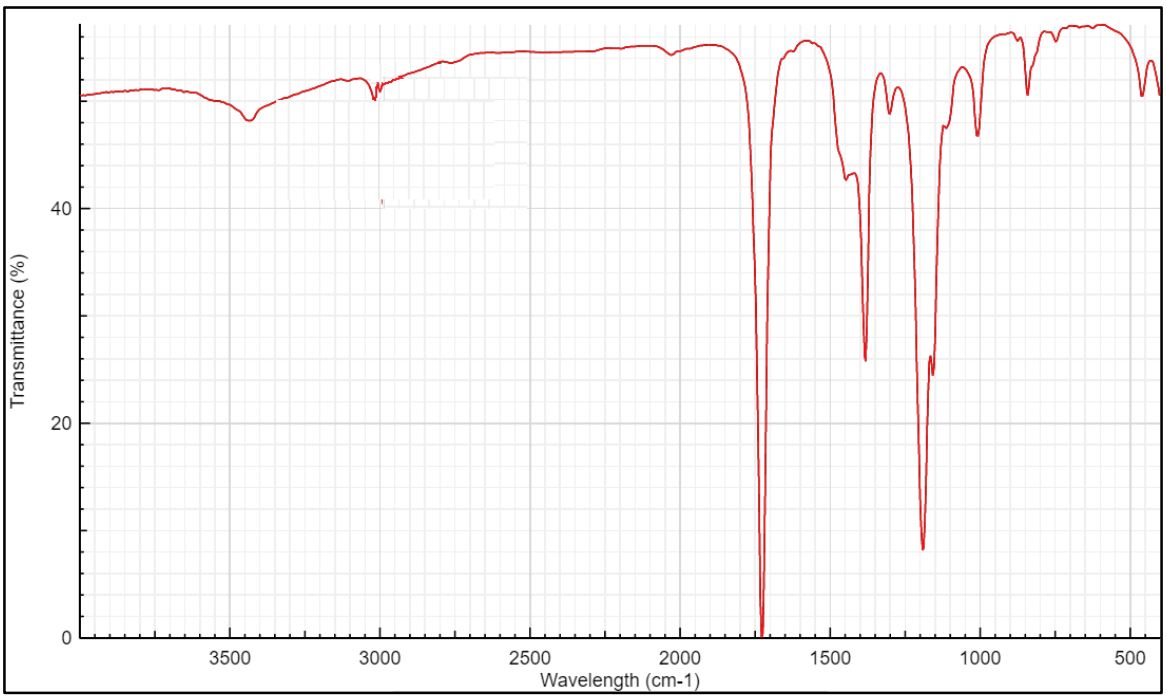
Element	(KeV)	Mass %	Error %	At %	K
O K	0.525	7.78	0.58	18.33	7.9679
Ep K	1.739	36.01	0.40	48.33	26.8751
Ed K	8.040	56.21	2.33	33.34	65.1570
Total		100.00		100.00	

FTIR analysis:



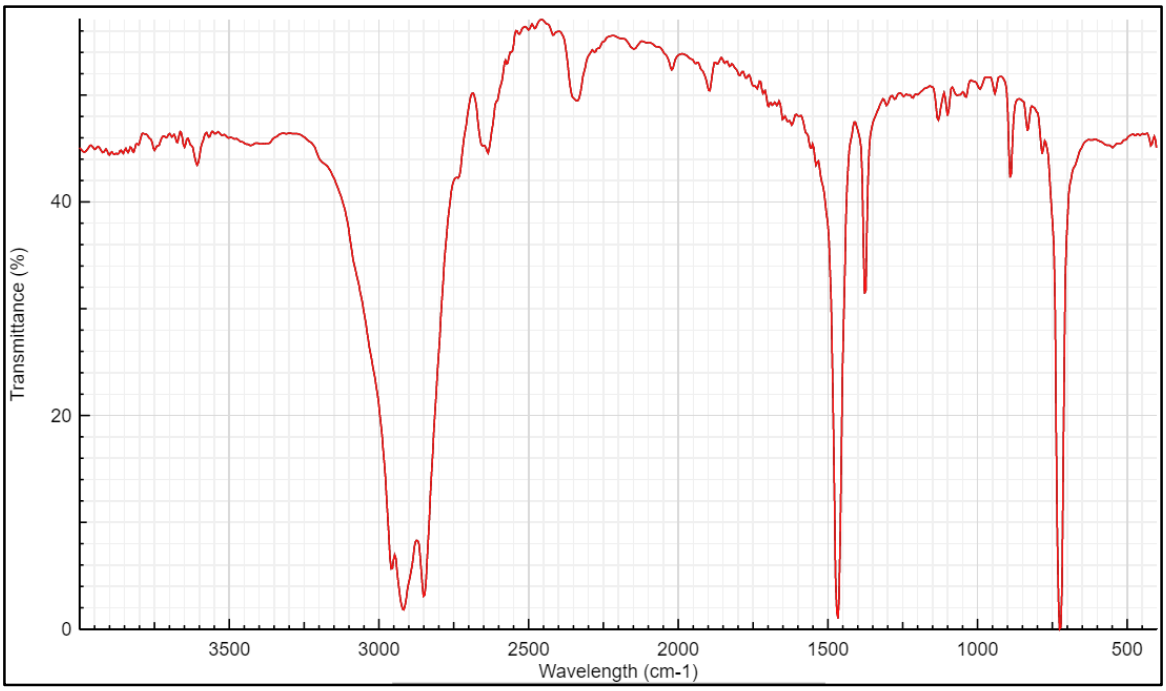
Spectrum 1 : IR of Candesartan

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretch	3471
2	-OH stretch	3234
3	=C-H Aromatic stretch	3041
4	=C-H Stretching	2962 2934 2876
5	-C=O stretching Conjugated vinyl bond	1706
6	-C-S linkage stretching	772



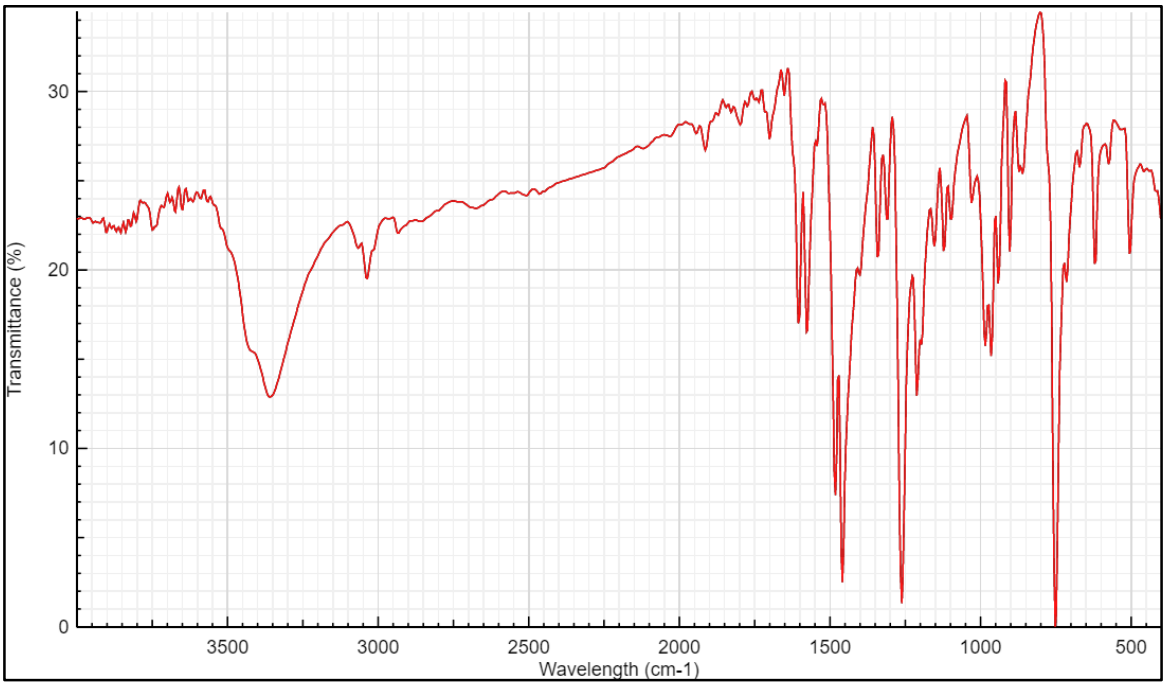
Spectrum : IR of Calcium Carbonate (Talc)

Sr.no	Functional group	Wave no.(cm^{-1})
1	-C=O stretching	1709
2	-C-O stretching	1229
3	=C-O Fingerprint	729



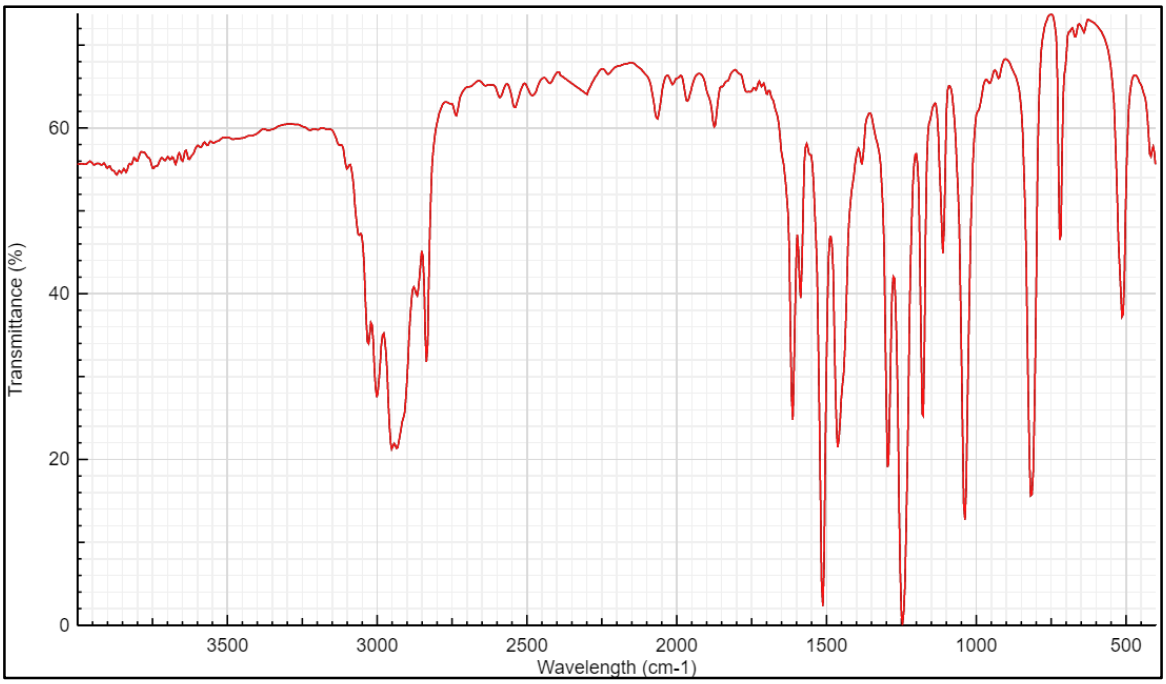
Spectrum : IR of Magnesium Stearate

Sr.no	Functional group	Wave no.(cm^{-1})
1	Carboxylate stretching	2917 2850
2	COO- Asymmetric twin bands	1497 1477



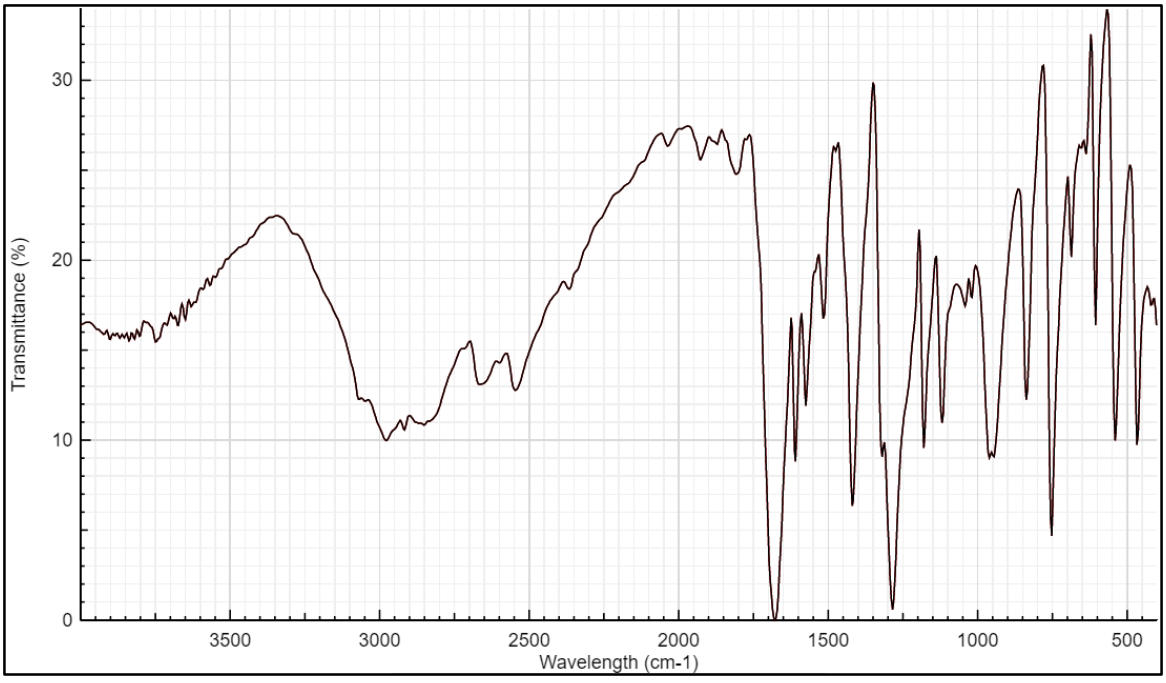
Spectrum : IR of Micro Cyrstalline Cellulose

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretching	3423
2	-CH stretching	2917
3	$-CH_2$ stretching	1479
4	-C-H stretching	1388
5	-C-O stretching	1210



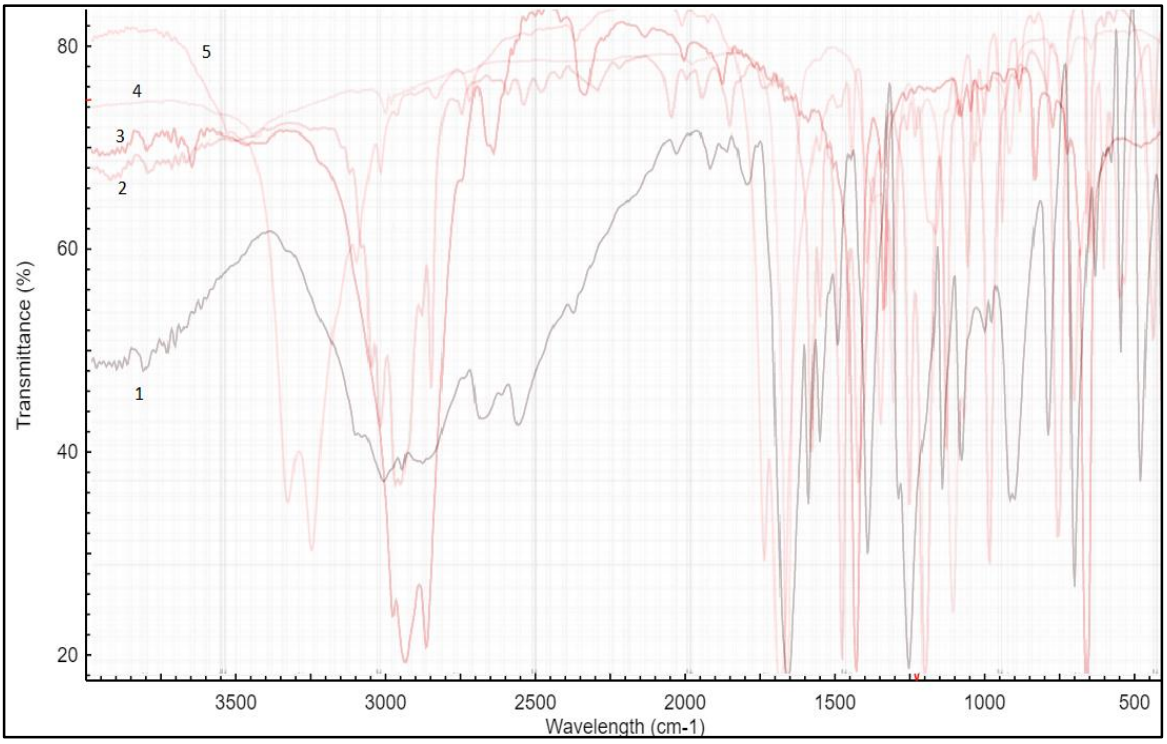
Spectrum : IR of Ethyl Cellulose

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretching	3126
2	-CH stretching	2987
3	$-CH_2$ stretching	1503
4	-C-H stretching	1387
5	-C-O stretching	1211



Spectrum : IR of Matrix Tablet

Sr.no	Functional group	Wave no.(cm^{-1})
1	-OH stretch	3040
3	=C-H Aromatic stretch	3041
4	=C-H Stretching	2962 2934 2876
5	-C=O stretching Conjugated vinyl bond	1706
6	-C-S linkage stretching	772



Spectrum : Overlay of FTIR Spectrum

Note: In overlay No 1 is spectrum of matrix tablet with excipients and No.2 ,3 , 4, 5 are Ethyl cellulose, Magnesium stearate, drug and Talc respectively.

13)CONCLUSION :

Oral drug administration is the most used method of administering medications. The goal of creating a matrix tablets formulation of a medication is to improve the treatment of the ailment while maximizing the therapeutic advantages and reducing the adverse effects. Angiotensin II receptor antagonists like candesartan are used to treat hypertension. It affects the renin-angiotensin system in two ways. Vasodilation happens when vascular smooth muscle relax and angiotensin II is unable to bind to AT1. The level of blood pressure decreases even more by preventing the synthesis of norepinephrine. The half-life of candesartan is five to nine hours. FT-IR frequencies, solubility tests, and organoleptic characteristics demonstrated that the Candesartan utilized was comparable to the levels that had been published. It was determined that there was indeed no drug-polymer incompatibility after comparing the FTIR readings. In order to create nanoparticles for matrix tablets, Eudragit RL 100 was used as the polymer. Talc and magnesium stearate were utilized as lubricants, while the microcrystalline cellulose plus ethyl cellulose, which aid in the gradual erosion of the matrix from the tablet, were used to create six formulations utilizing the direct compression method in this study.

Pre-compression characteristics such bulk density, tapped density, angles of repose, compressibility index, and Hausner's ratio were assessed for each batch of formulations, and the findings fell within the acceptable range. Additionally, the produced formulations were assessed for in-vitro drug release studies, weight fluctuation, hardness, friability, and content homogeneity. 98% of the drug was determined to be present. It was discovered that the tablets' hardness ranged from 4.6 to 5.3 kg/cm2. A friability of less than 1% suggested that the tablets had strong mechanical resistance.

Formulation F5 had the highest percentage cumulative release of drugs of candesartan, according to the in-vitro / experimental drug released data. In 12 hours, 98% of the medication was released by F5. The medication was released using zero order kinetics and anomalous (non-Fickian) release, according to the optimized formulation F5's "n" value of 0.4743. Complete release was

demonstrated by compositions F1, F2, F4, & F7 prior to 12 hours. The improved formulation remained stable in accelerated stability under temperatures of 40ºC and 75% relative humidity, according to the stability studies.

- The solvent evaporation approach was used to synthesize drug polymer nanoparticles. Wet impegration was used in the first stage, and a dry reduction reaction was used in the second. The following methods were used to confirm formation:

EDS analysis, SEM analysis, XRD analysis, and IR analysis.

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