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Formulation and Assessment of Candesartan Immediate Release Tablet by Direct Compression Method

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KEYWORDS

Candesartan Cilexetil, Immediate Release Tablet, Superdisintegrants, Hypertension.

ABSTRACT:

The present work is aimed at developing and evaluating an immediate-release (IR) tablet of Candesartan Cilexetil using direct compression, with the objective of enhancing its dissolution rate and oral bioavailability, as the drug is poorly soluble in water. Candesartan belongs to the Biopharmaceutical Classification System (BCS) class II, showing high permeability but limited solubility, making dissolution the rate-controlling step for absorption. This limitation is particularly important in hypertension therapy, where a rapid onset of action is crucial.

The formulation approach employed a combination of natural superdisintegrant (Isapghula husk) and synthetic superdisintegrant (Sodium Starch Glycolate) in varying ratios, along with conventional excipients such as Avicel PH 102, lactose monohydrate, talc, and magnesium stearate. Preformulation studies, including melting point determination, UV spectroscopic analysis, FTIR compatibility testing, and solubility assessment, confirmed the purity and stability of the drug–excipient mixture.

Evaluation of post-compression parameters involved determination of hardness, friability, disintegration time, drug content uniformity, and in vitro release behaviour. Among all prepared batches, formulation F5 was found to be superior, as it showed the shortest disintegration time and maximum drug release. The release profile was best explained by first-order and Higuchi models, suggesting that the drug release followed a diffusion-controlled mechanism.

Overall, this investigation demonstrates that direct compression is a simple, reliable, and scalable technique for producing immediate-release Candesartan tablets, with the potential to improve patient compliance and therapeutic efficacy in the treatment of hypertension.

1 Introduction

1.1 General introduction

A variety of factors make oral administration the most preferred and widely accepted route for producing systemic therapeutic effects. This preference is primarily due to its convenience, non-invasiveness, absence of pain, and overall better patient compliance compared to other administration routes. Additionally, the oral route offers versatility in formulation design and ensures higher levels of patient acceptance. From a manufacturing standpoint, oral solid dosage forms are cost-effective to produce, as they do not demand sterile conditions during large-scale production. Among the available oral solid dosage forms, tablets are regarded as the most ideal because they ensure accurate dosing, improved patient adherence, and enhanced efficiency in production. [1, 2].

1.2 Hypertension:

The threshold values used to diagnose hypertension vary according to the measurement technique applied. Several determinants contribute to the onset of hypertension. Nearly 90–95% of affected individuals present with

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JCHR (2025) 15(5), 1571-1579 | ISSN:2251-6727

primary, also termed "essential," hypertension, which arises from a complex interaction of genetic and environmental influences. A positive family history is commonly observed, and research estimates the heritability—defined as the proportion of variation in the trait attributable to genetic factors—between 35% and 50% [3, 4].

Blood pressure values as low as 115/75 mmHg, which is well within the normotensive range, are the starting point for the graded and ongoing association between blood pressure and an increased risk of cardiovascular disease.

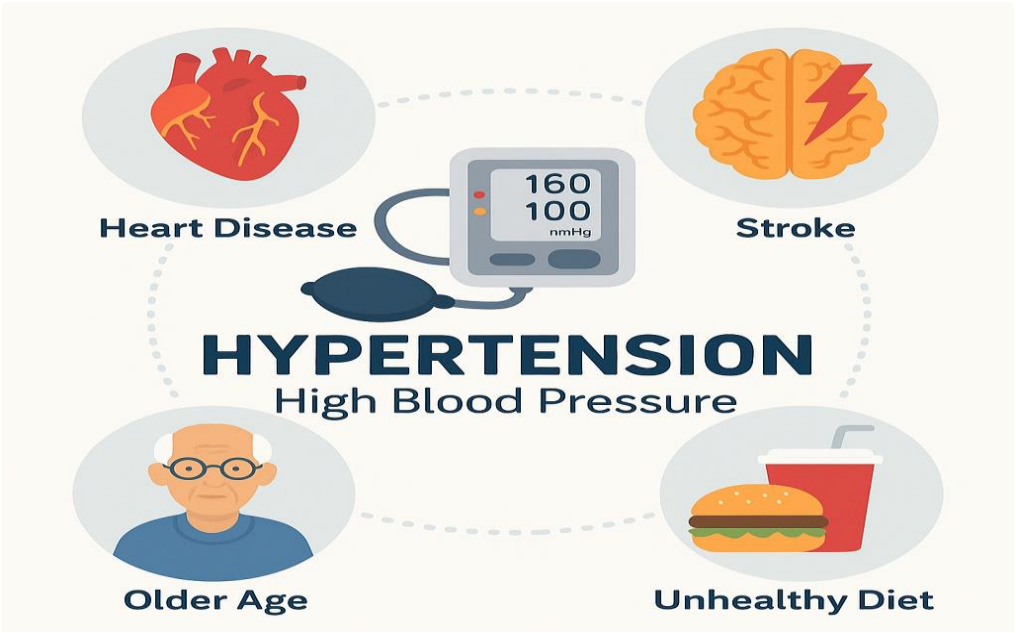

Figure: 1 Hypertension: Risk Factors and Health Impact Overview [5]

1.3 Candesartan:

Candesartan is a therapeutic agent that belongs to pharmacological class of angiotensin II receptor antagonists, commonly referred to as angiotensin receptor blockers (ARBs). These agents are highly recognized for their role in management of cardiovascular & renal disorders, including hypertension, diabetic nephropathy, myocardial infarction, and chronic heart failure.

Candesartan itself is a non-peptide, tetrazole-derived compound, primarily administered orally.

It is considered a highly potent and selective ARB with no partial agonist activity, which enhances its efficacy in blood pressure control [6].

1.4 Advantages of Immediate Release

- Cost-efficient and economical. Rapid beginning of action.
- Appropriate for industrial manufacturing.
- Enhanced stability and bioavailability.
- Enumerates some benefits of liquid dosage types.

1.5 Disadvantages of IR Tablets [7]

- Immediate pharmacological treatment intervention is unfeasible.
- Occasionally necessitates increased frequency of administration.
- Dose dumping may transpire.
- Decreased capacity for precise dosage modificatio**2. Methodology**

2.1 Materials:

All chemicals and reagents utilized were of analytical or medicinal quality. Excipients were chosen for their adherence to pharmacopeial standards and compatibility with the active pharmaceutical ingredient (API).

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2.2 Pre formulation study:

A. Melting point determination:

A little quantity (about 2–3 mm) of the finely powdered substance was inserted into a capillary tube sealed at one end. A tube was thereafter positioned in a melting point apparatus adjacent to a calibrated thermometer. Sample was incrementally heated, and the temperature at which the medication commenced melting (onset) & temperature at which it fully liquefied (clear point) were documented. Melting point was documented as a limited range between these two temperatures. [8]

B. Identification of pure drug by UV spectroscopy:

Procedure:

A standard solution of Candesartan was prepared in methanol or phosphate buffer. The λmax was determined by scanning the spectrum from 200 to 400 nm. The obtained spectrum was compared with recorded values. [9]

C. Drug excipients compatibility study:

Excipients are integral to almost every pharmaceutical dosage form. Developing a reliable and stable solid formulation requires careful selection of these components, as they aid in drug administration, support uniform release & bioavailability, and protect the active substance from degradation. [10]

D. Fourier Transform Infrared Spectroscopy (FTIR):

A FTIR spectroscopic study was performed to eliminate potential for drug-excipient interactions during formulation using the direct compression method. FTIR spectra were obtained in the range of 4000-500 cm-1 for both the drug alone and drug combined with excipients. [11]

F. Determination of solubility:

Candesartan's solubility in water, PEG 400, and propylene glycol was examined by making saturated solutions with more medication and stirring them for a full day. Samples were diluted and subjected to UV spectrophotometry at 257 nm following filtering. Using a calibration curve, the drug's solubility in each solvent was ascertained. This technique made sure that the solubility of candesartan in various vehicles was measured accurately. [12, 13]

2.3 Formulation of candesartan tablets:

Sieving of Components, Sift all ingredients, except magnesium stearate and talc, through a 40 mesh sieve to ensure uniform particle size and remove lumps. Separate magnesium stearate & talc by sifting each through a 60 mesh screen. Preparation of Drug-Excipient Combination. Accurately quantify the required quantities of the pharmaceutical and excipients. Utilized a mortar and pestle or a polybag to amalgamate the sieved powders employing the geometric dilution technique for about 10–15 minutes to ensure homogeneous medication distribution. Integration of Glidant and Lubricant, Add talc to the powder mixture and stir for 3 to 5 minutes. Finally, incorporate magnesium stearate and blend gently for a further 2–3 minutes to avoid excessive lubrication, which might undermine tablet hardness and disintegration. Employ a single-punch or rotary tablet compression apparatus to compress the finished mixture into tablets. Employ flat-faced punches, typically 8–10 mm in diameter, depending on size of the target tablet & dose required. [14, 15]

2.4 Evaluation of candesartan tablets:

1. Pre-compression parameters: were assessed to examine the flow and packing characteristics of the powder blend. The angle of repose was determined by permitting the powder to discharge from a funnel, creating a heap, and calculating the angle using $\tan\theta = h/r$, with the results averaged across three attempts. Subsequently, bulk density (BD) was ascertained by introducing a specified weight of powder into a graduated cylinder and calculating $BD = M/Vb$ without tapping, so preventing compaction. The tapped density (TD) was determined by tapping the cylinder until the volume stabilised, followed by calculating $TD = M/Vt$. The Carr's index (CI) was determined using the formula $CI = (TD - BD)/TD \times 100$ to evaluate compressibility, while Hausner's ratio (HR) was computed with $HR = TD/BD$ as a supplementary flow measure, with all experiments conducted in triplicate and average values presented [16].

2. Post compression parameters: [17, 18]

Tablet Thickness

12 tablets were randomly chosen from the formulas, & their thickness was tested separately. The measurement

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JCHR (2025) 15(5), 1571-1579 | ISSN:2251-6727

was articulated in mm by vernier caliper, and the average was calculated.

3. Tablet Hardness

The ability of a tablet to tolerate mechanical shocks while handling is indicated by its hardness. A Monsanto hardness tester was used to assess the tablets' hardness. The unit of measurement was kg/cm². To test the hardness of each formulation, ten tablets were chosen at random. Additionally, the mean value was calculated.

4. Friability:

The tablets' friability was assessed with a Roche friabilator and reported as a percentage. A sample of tablets weighing approximately 6.5 g (W initial) was subjected to a friabilator operating at 25 revolutions per minute for 4 minutes, totalling 100 revolutions. Subsequent to the test, the tablets were extracted, purged of any loose particulate matter, and reweighed to ascertain the final weight (W final).

7. Disintegration:

The beaker of the disintegration apparatus was filled with 900 mL of freshly prepared distilled water or phosphate buffer (pH 6.8). Medium temperature was maintained at 37 ± 2 °C using a water bath. 1 tablet was placed in each of 6 tubes of disintegration basket. If specified in monograph, a disc was positioned over each tablet to prevent floating. The basket was then immersed into the medium, and the instrument was switched on to begin the test. [19]

8. in Vitro Drug Dissolution Studies [20]

Using a USP type II dissolution device in sink conditions, the in vitro drug release of candesartan from various formulations was assessed. 900 mL of phosphate buffer (pH 6.5) with 0.35% polysorbate 20 made up the

3 Results

3.1 Preformulation Studies

A. Melting Point Determination

Melting point of Candesartan Cilexetil was observed between 168°C to 170°C, which aligns with literature

5. Weight Variation

A total of 20 tablets were selected at random, weighed, &their mean weight was calculated. The weight of each tablet was then determined individually. According to USP specifications, weight of any single tablet should not be less than 90% and not more than 110% of the calculated average weight.

6. Drug Content Estimation

20 tablets were weighed and pulverised into a fine powder. An accurately measured quantity of this powder, according to the weight of five tablets, was put into a 100 mL volumetric flask. A minimal quantity of methanol was introduced to dissolve the contents, and the volume was calibrated to 100 mL with methanol prior to filtration. From this filtrate, 10 mL was extracted and diluted to 100 mL with phosphate buffer (pH 6.5) containing 0.35% polysorbate 20. The solution was properly mixed, and its absorbance was measured at 257 nm with a UV spectrophotometer.

dissolution media, which was kept at 37 ± 0.5 °C. To replicate gastrointestinal conditions, the paddle speed was set at 50 rpm. After testing each formulation for an hour, 5 mL samples were taken out at prearranged intervals, filtered through Whatman filter paper, and then refilled with an equivalent volume of new buffer to keep the volume constant. A UV spectrophotometer was used to determine the samples' candesartan concentration at 257 nm.

9. Release kinetics modules

Different mathematical models were applied to study release kinetics of drug from various RST formulations. The models used for analysing the release pattern included the Korsmeyer–Peppas model, the First-order kinetic model, and the Higuchi model.

values. A narrow melting point range indicates good purity and crystalline nature of the drug.

B. UV Spectroscopy

The maximum absorbance (λmax) of the drug was observed at 257 nm in methanol and phosphate buffer (pH 6.8), which matches the standard λmax reported for Candesartan Cilexetil, confirming its identity.

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Table: 3.1 Calibration Data Table for Candesartan Cilexetil (λmax = 257 nm)

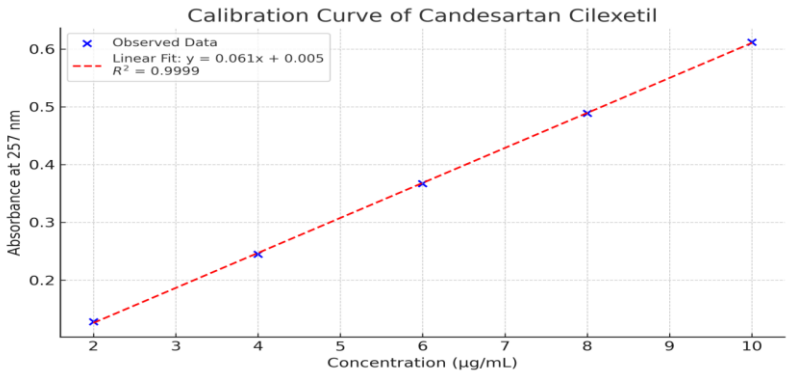
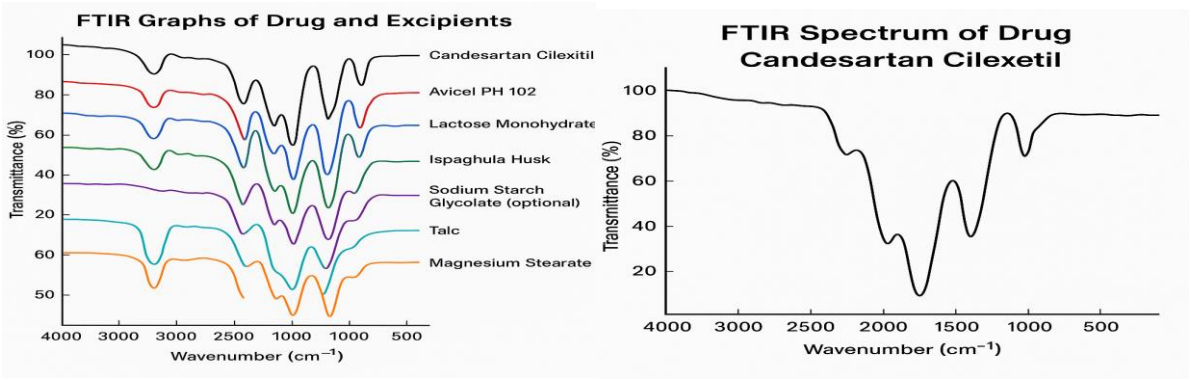


Figure: 2 Calibration Curve Drug (Absorbance vs. Concentration)

3.1.3 Drug-Excipients Compatibility (FTIR Study)

The FTIR spectra of Candesartan alone and its physical mixture with excipients were compared. The key peaks of the drug remained unaltered in physical mixture

3.1.5 FTIR of Drug + Excipients Physical Mixture



(A) **(B)**

Figure: 3 (A), (B) of FTIR of Pure drug and excipients mixture

C. Solubility Study

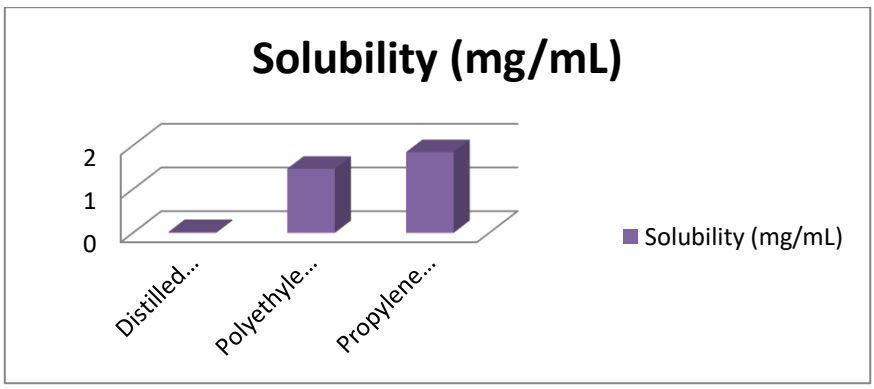


Figure: 4 Graph of Solubility of drug in various solvents

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3.2 Evaluation of Pre-Compression Parameters

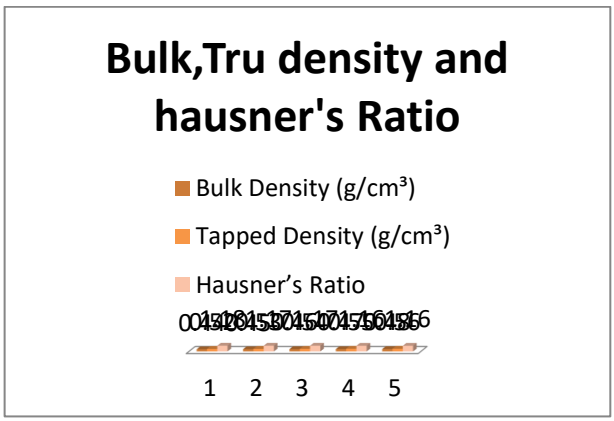

Figure: 4 Graphical Representation of the Micromeretics study of powder

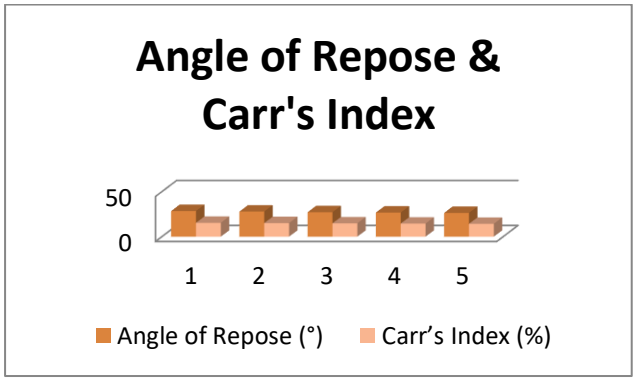

Figure: 5 Graph of Micromeretics Study of the powder

3.3 Evaluation of Post-Compression Parameters

Table: 3.5 Post Compression Evaluation of tablet

Formulation	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Average Weight (mg)	Weight Variation (mg)
F1	3.14 ± 0.05	4.5 ± 0.10	0.48 ± 0.01	200 ± 1.56	±3.12
F2	3.16 ± 0.06	4.6 ± 0.12	0.42 ± 0.02	199 ± 1.72	±3.44
F3	3.18 ± 0.03	4.7 ± 0.15	0.39 ± 0.02	201 ± 1.61	±3.22
F4	3.19 ± 0.04	4.8 ± 0.18	0.35 ± 0.01	200 ± 1.58	±3.16
F5	3.21 ± 0.05	5.0 ± 0.17	0.31 ± 0.01	200 ± 1.47	±2.94

All tablet formulations (F1 through F5) exhibit consistent thickness, hardness, friability, and weight parameters, according to the post-compression examination. It has strong mechanical strength, with thickness ranging from 3.14 mm to 3.21 mm and hardness ranging from 4.5 to 5.0 kg/cm². When friability scores are less than 0.5%, tablets appear to be robust and unlikely to shatter. With an average weight of about 200 mg and little variance, the dosage is consistent among formulations. All things considered, the tablets are up to par.

3.4 Drug Content Uniformity and Disintegration Time

Table: 3.7 Tablet Drug content and Disintegration Time

Formulation	Drug Content (%)	Disintegration Time (sec)
F1	97.32 ± 0.35	180 ± 4.1
F2	98.12 ± 0.29	145 ± 3.8
F3	99.06 ± 0.42	115 ± 3.2
F4	99.28 ± 0.38	90 ± 2.6

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F5	99.45 ± 0.25	60 ± 2.1

The high drug concentration (97.32% to 99.45%) in all tablet formulations suggests consistency. In later formulations, the disintegration time improves from 180 seconds (F1) to 60 seconds (F5), indicating quicker drug release. F5 has the fastest disintegration and the highest content.

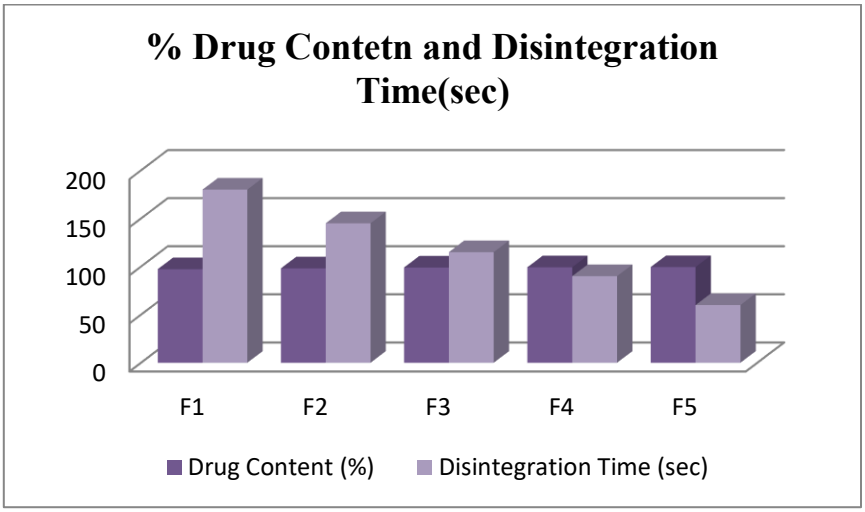

Figure: 6 graphically representation of Disintegration and % Drug Content of Candesartan cilexetil

3.5 In Vitro Drug Dissolution:

The drug release data indicates a significant enhancement in the release rate from F1 to F5. At 60 minutes, F1 released 85% of the medication, whereas F5 released 99.5%, signifying practically total drug release. The improvement in drug release from F1 to F5 is due to improved formulation factors, including enhanced disintegration time and efficient use of superdisintegrants. F5 demonstrated the most quick and substantial release, indicating superior dissolving properties and positioning it as the most promising formulation for fast therapeutic efficacy.

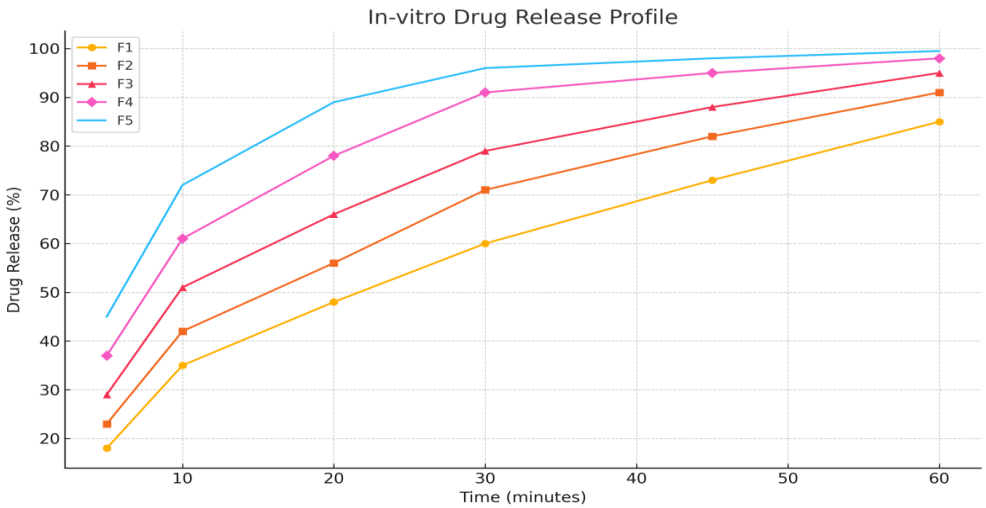

Figure: 7 Graph of in-Vitro Drug Release Profile

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3.6 Drug Release Kinetics

Table: 3.9 various release kinetics modules

Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas n
F1	0.940	0.971	0.981	0.49
F2	0.945	0.975	0.983	0.48
F3	0.956	0.982	0.986	0.47
F4	0.964	0.988	0.990	0.46
F5	0.972	0.992	0.993	0.45

According to the release kinetics analysis, the Higuchi model fits all formulations the best (R2 up to 0.993), indicating diffusion-controlled drug release. Additionally, there is a high connection in first-order kinetics, particularly in F5 (R2 = 0.992), which suggests concentration-dependent release. Across formulations, a non-Fickian diffusion mechanism is suggested by the Peppas n values (0.45–0.49). F5 exhibits the most reliable and regulated release behaviour overall.

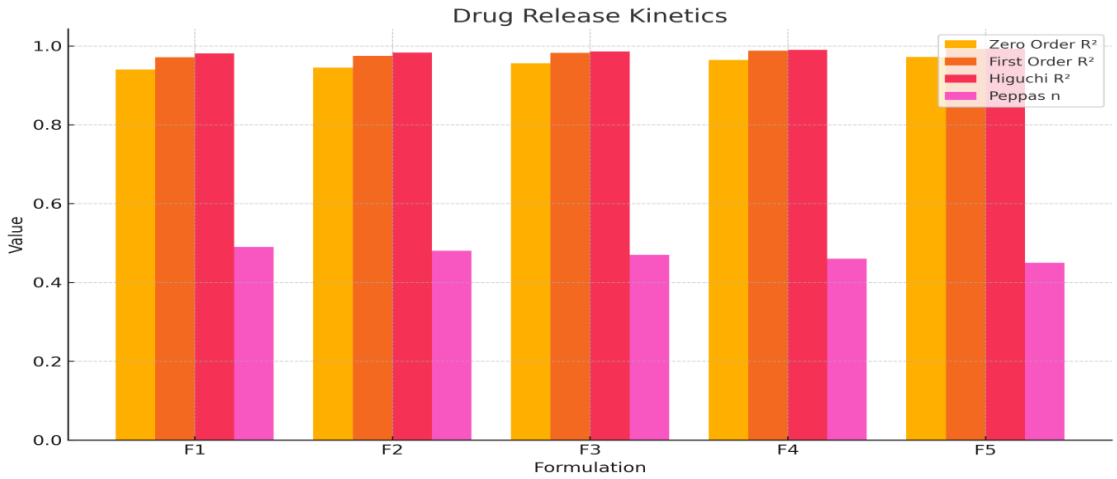

Figure: 8 Graph of Release Kinetics

Conclusion:

The research effectively developed and assessed IR tablets of Candesartan Cilexetil via the direct compression method. aim was to rectify the drug's inadequate solubility and protracted therapeutic response by improving its dissolution rate and disintegration properties. Of the five formulations created (F1–F5), F5 exhibited exceptional performance in all metrics, including optimal tablet thickness (3.21 mm), maximum hardness (5.0 kg/cm²), minimal friability (0.31%), swift disintegration, and peak drug release (~98% within 30 minutes). The amalgamation of natural (Isapghula husk) and synthetic (SSG) superdisintegrants shown significant efficacy in improving the dissolving profile.

Preformulation and FTIR analyses verified the absence of incompatibility between the medication and excipients, hence assuring formulation stability. The drug release kinetics adhered to Higuchi and first-order models, signifying a diffusion and concentration-dependent release mechanism.

The optimised IR tablet provides a quick therapeutic response, is economically viable, and exhibits significant scalability, rendering it appropriate for mass production and perhaps enhancing adherence among hypertensive

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patients necessitating immediate blood pressure regulation

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