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CO-CRYSTALLIZATION ENABLED CANDESARTAN CILEXETIL AND HYDRO-CHLOROTHIAZIDE TABLETS FOR IMPROVED BIO AVAILABILITY IN HYPERTENSION MANAGEMENT

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Keywords:

Hypertension, Candesartan cilexetil, Hydrochlorothiazide, Co-crystal, Urea, Solubility enhancement

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ABSTRACT: Background: Hypertension often requires combination therapy for effective control. The combined use of candesartan cilexetil and hydrochlorothiazide is limited by poor water solubility and low oral bioavailability. Co-crystallization with suitable co-formers can improve solubility and dissolution, thereby enhancing therapeutic efficacy. **Objective:** This study aimed to create and assess an immediate-release (IR) tablet containing co-crystals of Candesartan cilexetil and Hydrochlorothiazide, utilizing urea as a co-former to improve solubility and dissolution rate, thus enhancing bioavailability. **Methods:** Co-crystals of Candesartan–Urea and HCTZ–Urea were synthesized using the solution evaporation technique. The resulting co-crystals were analyzed using FTIR, and PXRD to verify co-crystal formation and evaluate compatibility. The optimized co-crystal mixtures were compressed into immediate-release tablets with superdisintegrants. The formulations underwent evaluation for pre- and post-compression parameters, *in-vitro* dissolution, and stability under ICH conditions. **Results:** The optimized formulation displayed excellent flow characteristics and consistent weight distribution. The immediate-release tablet disintegrated rapidly and showed significantly improved dissolution compared to the pure drugs. The dissolution data adhered to Hixson–Crowell kinetics, indicating uniform drug release through surface erosion. FTIR and PXRD confirmed co-crystal formation without chemical interaction between the drug and excipients. Stability studies revealed no significant changes in drug content, hardness, friability, or release profile after 30 days. **Conclusion:** The developed Candesartan–HCTZ co-crystal immediate-release tablets showed improved solubility and dissolution with good physical and chemical stability, highlighting co-crystallization as an effective strategy to enhance the bioavailability of poorly soluble antihypertensive drugs.

INTRODUCTION: Drug delivery systems influence how drugs are formulated and delivered to achieve optimal therapeutic outcomes. Oral drug delivery remains the most preferred route due to its convenience, patient compliance, and formulation flexibility [1].

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Hypertension is a major global health concern, defined by persistently elevated blood pressure (≥140/90 mmHg), and often requires long-term combination therapy [2, 3].

The fixed-dose combination of Candesartan Cilexetil and Hydrochlorothiazide (HCTZ) is widely used for its synergistic antihypertensive effect; however, its clinical efficacy is limited by poor aqueous solubility and low oral bioavailability, particularly of Candesartan Cilexetil. Conventional formulations, being simple physical mixtures, fail to adequately address these limitations.

Co-crystallization offers a promising strategy to enhance the physicochemical properties of poorly soluble drugs without altering their pharmacological activity. This study focuses on the development of Candesartan Cilexetil–HCTZ co-crystals using GRAS-status co-formers such as urea to improve solubility and dissolution. The optimized co-crystals are formulated into tablets and evaluated for solid-state properties, dissolution behavior, and tablet performance, providing a potential alternative to traditional fixed-dose antihypertensive formulations.

Co-Crystal Formulation [4-5]: Co-crystallization has emerged as an effective strategy in pharmaceutical formulation to tackle solubility issues. Co-crystals consist of multicomponent crystalline structures formed by a co- former and an API, linked through non-covalent interactions, especially hydrogen bonds. These co-crystals are suitable for BCS Class II and IV drugs as they can enhance solubility, dissolution rate, mechanical stability, and even bioavailability.

Pharmaceutical co-crystals are solid-state formations composed of a neutralco-former and an API in a defined stoichiometric ratio, held together by non-covalent forces such as π–π stacking, hydrogen bonding, and van der Waals interactions. While modifying the drug's physicochemical properties, particularly solubility, dissolution rate, and mechanical behavior, co-crystals maintain the drug's chemical identity. The therapeutic effectiveness of numerous active pharmaceutical ingredients (APIs) can be hindered by challenges like low aqueous solubility, slow dissolution rate, and limited bioavailability.

Co-crystal formulation offers a promising approach to overcome these limitations without altering the API's chemical structure. One of the primary advantages of co-crystals is their ability to enhance the solubility and dissolution rate of poorly water-soluble drugs, leading to improved bioavailability and faster absorption in the gastrointestinal tract. Consequently, treatment may become more effective at lower doses.

MATERIALS AND METHODS:

Materials & Instruments: The drug substances, excipients, and chemicals required for the formulation of candesartan cilextil and Hydrochlorothiazide co crystal IR tablets were kindly provided by Saimirra Innopharm Pvt. Ltd., India. And urea provided by central leather research institute. All materials used were of pharmaceutical/analytical grade. All instruments and equipment required for the formulation and evaluation studies were made available and utilized at the facilities of Saimirra Innopharm Pvt. Ltd. (India).

Preformulation Studies: Candesartan cilexetil and hydrochlorothiazide (HCTZ) were subjected to preformulation studies to confirm identity, purity, and suitability for co-crystal formulation. Physical appearance and crystalline nature were visually examined. Solubility was assessed in water, phosphate buffer (pH 6.8), acetone, ethanol, and methanol. Melting points were determined and compared with reported literature values.

UV spectrophotometric analysis was performed using methanol as solvent. The λmax values were identified at 254 nm for candesartan cilexetil and 271 nm for HCTZ. Calibration curves (2–10 µg/mL) were prepared, and a validated simultaneous equation method was employed for quantitative estimation. Drug excipient compatibility was evaluated using FTIR spectroscopy, while PXRD analysis was performed to establish the crystalline nature of the pure drugs.

Preparation of Co-Crystals: Binary co-crystals of candesartan cilexetil–urea and HCTZ–urea were prepared in molar ratios of 1:1, 1:2, and 1:3 using the solution evaporation method. Accurately weighed quantities of API and urea were dissolved in a methanol: acetone (1:1, v/v) solvent system under continuous stirring. The clear solution was filtered and concentrated using a rotary evaporator. Slow solvent evaporation at room temperature facilitated crystal formation. The obtained co-crystals were dried under vacuum at 30 °C and stored in desiccators until further use. Equilibrium solubility studies in phosphate buffer (pH 6.8) were conducted for all batches, and the 1:2 molar ratio for both drugs was selected as the optimized co-crystal based on maximum solubility enhancement.

Characterization of Optimized Co-Crystals: The optimized co-crystals were characterized using

PXRD to confirm the formation of a new crystalline phase. FTIR spectroscopy was used to identify intermolecular interactions between the API and co-former. Equilibrium solubility and in-vitro dissolution studies were performed in pH 6.8 phosphate buffer to assess improvements in solubility and dissolution behaviour compared to the pure drugs.

Formulation of Immediate-Release Tablets: The optimized candesartan–urea and HCTZ–urea co-crystals were formulated into matrix immediate-release (IR) tablets by direct compression. Each tablet had a total weight of 300 mg and contained co-crystals equivalent to the labelled doses of candesartan cilexetil and HCTZ. Microcrystalline cellulose, mannitol, hydroxypropyl cellulose, aerosil, magnesium stearate, and super disintegrants (crospovidone, croscarmellose sodium, or sodium starch glycolate at 2.5% and 5%) were used. All ingredients, except magnesium stearate, were sieved, blended uniformly, lubricated, and compressed using a rotary tablet press fitted with a 9 mm punch.

Evaluation of Tablets:

Pre-Compression Evaluation: Powder blends were evaluated for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio to assess flow and compressibility.

Post-Compression Evaluation: Compressed tablets were evaluated for appearance, thickness, weight variation, hardness, friability, and disintegration time as per pharmacopeial standards.

Drug Content Uniformity: Drug content was determined using the validated simultaneous estimation method, and results were expressed as a percentage of the labelled claim.

***In-vitro* Dissolution Studies:** Dissolution studies were performed using USP Type II (paddle) apparatus at 50 rpm in phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C. Samples were withdrawn at predetermined time intervals and analysed spectrophotometrically.

Release Kinetics: Dissolution data of the optimized formulation were fitted to the Hixson–Crowell cube-root model using DD-Solver software to determine the drug release mechanism.

Stability Studies: Stability studies were conducted in accordance with ICH guidelines under room temperature and accelerated conditions (40 °C ± 2 °C / 75% ± 5% RH). Tablets were evaluated for physical appearance, hardness, friability, drug content, and dissolution behavior.

RESULTS:

Preformulation Studies (Characterization of Drug Substances): The samples of candesartan cilextil and Hydrochlorothiazide were characterized by various parameters to ensure their identity, purity and suitability for formulation.

Physical Appearance:

Candesartan cilexetil: White to off white, crystalline powder

Hydrochlorothiazide: white, Crystalline powder

Solubility:

Candesartan cilexetil: Candesartan cilexetil exhibited very low aqueous solubility, showing slightly improved solubility in phosphate buffer (pH 6.8), moderate solubility in acetone, and good solubility in organic solvents such as ethanol and methanol [6-9].

Hydrochlorothiazide: hydrochlorothiazide was sparingly soluble in water, showed relatively higher solubility in phosphate buffer (pH 6.8), moderate solubility in acetone, and enhanced solubility in ethanol and methanol [10-13].

Determination of Melting Point (M.P): The melting point of Candesartan cilexetil was found to be 166 °C, and for Hydrochlorothiazide 270 °C, which were in close agreement with the reported literature values, confirming the identity and purity of the obtained drug samples [14-15].

UV-Spectroscopy: The λmax of Candesartan cilextil and Hydrochlorothiazide were determined by scanning standard solutions (10 µg/mL) in the wavelength range of 200–400 nm using methanol. The λmax was found to be 254 nm for Candesartan cilexetil and 271 nm for Hydrochlorothiazide, which were used for quantitative analysis.

Calibration Curve & Simultaneous Estimation: Standard stock solutions of Candesartan cilexetil and Hydrochlorothiazide were prepared separately

in methanol and diluted to obtain concentrations in the range of 2–10 µg/mL. The absorbances of each solution were measured at 254 nm and 271 nm to account for spectral overlap and to enable simultaneous estimation of both drugs **Table 1.** Calibration curves were constructed by plotting absorbance against concentration. Candesartan cilexetil showed linearity at 254 nm, while Hydrochlorothiazide exhibited linearity at 271 nm, as shown in **Fig. 1** and **Fig. 2,** respectively.

Both drugs demonstrated excellent linearity over the studied concentration range with correlation coefficients ($R^2 > 0.99$), confirming the suitability of the method for quantitative and simultaneous estimation in the co-crystal IR tablet formulation. The concentrations of both drugs in the combined dosage form were calculated using the simultaneous equation method, based on absorptivity coefficients determined at both wavelengths **Table 2.**

TABLE 1: CALIBRATION CURVE OF CANDESARTAN CILEXETIL AND HYDROCHLOROTHIAZIDE

Calibration Curve for Candesartan Cilexetil			Calibration curve for HCTZ	
Concentration (µg/ml)	Absorbance (nm)		Absorbance (nm)	
	254	271	254	271
0	0.001	-0.0001	0.001	-0.0001
2	0.054	0.024	0.054	0.024
4	0.121	0.042	0.121	0.042
6	0.193	0.071	0.193	0.071
8	0.259	0.095	0.259	0.095
10	0.323	0.12	0.323	0.12

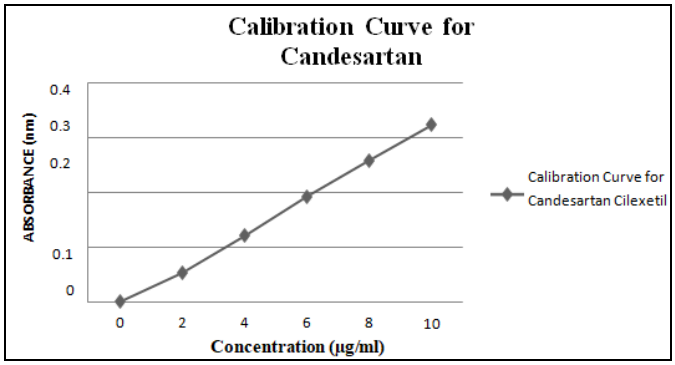

FIG. 1: CALIBRATION CURVE OF CANDESARTAN CILEXETIL AT 254NM (N =3)

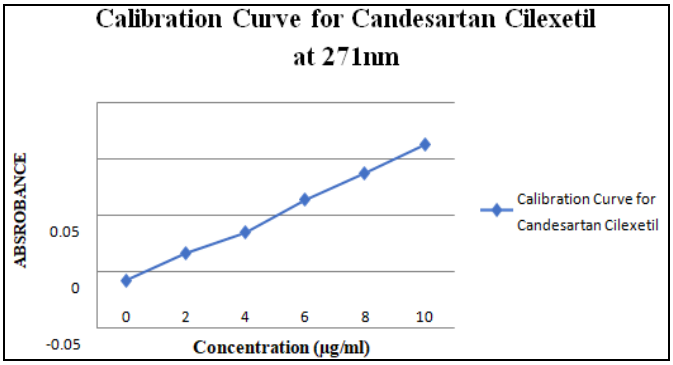

FIG. 2: CALIBRATION CURVE OF CANDESARTAN CILEXETIL AT 271NM

Candesartan = $(A_2b_1-A_1b_2) / (a_1b_2-a_2b_1)$ CHCTZ = $(A_1a_2-A_2a_1) / (a_1b_2-a_2b_1)$ A_1 and A_2 are the absorbance of the mixture at 260nm and 288nm respectively.

a_1, a_2 = absorptivity of Candesartan Cilexetil at 254 and 271 nm b_1, b_2 = absorptivity of Hydrochlorothiazide at 254nm and 271 nm.

TABLE 2: ABSORPTIVITY COEFFICIENTS VALUE

Drug	At 254nm	At 271nm
Candesartan Cilexetil	a1=0.0322	a2=0.0120
Hydrochlorothiazide	b1=0.0190	b2=0.0680

Drug-Excipient Compatibility Study: FTIR spectra of Candesartan Cilexetil and Hydrochlorothiazide, and their physical mixtures with excipients were recorded using a KBr pellet method in the range of 4000–400 cm^{-1} to evaluate potential drug-excipient interactions [16, 17].

Powder X-ray Diffraction (PXRD) [18]: The analysis was performed for the pure APIs (Candesartan cilexetil and Hydrochlorothiazide) and their prepared co-crystals to evaluate crystallinity and confirm co-crystal formation. Samples were scanned in the 2θ range of 5°–50° using Cu Kα radiation (λ = 1.5406 Å). Distinct characteristic peaks of the pure drugs were compared with those of the co-crystals. The appearance of new diffraction peaks and changes in intensity or position of existing peaks indicated the

formation of a new crystalline phase, confirming successful co-crystallization.

Solubility Studies for Co-crystal [19]: The equilibrium solubility of all Candesartan–Urea (1:1, 1:2, 1:3) and Hydrochlorothiazide– Urea (1:1, 1:2, 1:3) co-crystal batches was determined in phosphate buffer (pH 6.8) at 37 ± 0.5 °C using the excess solid method. Excess amounts of each sample were added to 10 mL of medium and shaken for 48 hours in a thermostatically controlled orbital shaker to achieve equilibrium. The mixtures were filtered through 0.45 µm membrane filters, suitably diluted, and analyzed spectro-photometrically at 254 nm for Candesartan Cilexetil and 271 nm for HCTZ. The solubility, expressed in µg/mL, was used to identify the 1:2 co-crystal ratio of both drugs as the optimized batch for further formulation studies.

Preparation of Binary Co-crystals by Solution-Evaporation Method [20, 21]: Binary co-crystals of Candesartan Cilexetil Urea and Hydrochlorothiazide Urea were prepared at molar ratios of 1:1, 1:2, and 1:3 using a solution evaporation technique. For each batch, the accurately weighed API and urea (as per **Table 3** and **4** were dissolved in a methanol: acetone (1:1, v/v) solvent system under continuous stirring at 25–30 °C. Additional solvent was added incrementally, if required, to obtain a clear solution. Gentle warming (not exceeding 35 °C) or brief sonication was employed when necessary. The resulting clear solution was filtered and concentrated under reduced pressure at 30–35 °C using a rotary evaporator until nucleation was observed, followed by slow solvent evaporation at room temperature to allow crystal growth. The formed co-crystals were collected and dried under vacuum at 30 °C to constant weight to avoid polymorphic transformation. Dried samples were stored in labeled amber vials in a desiccator until further use. Co-crystals prepared as described above were subjected to solubility studies, solid-state characterization (PXRD and FTIR), and dissolution evaluation to identify the optimized molar ratio for each drug. The optimized co-crystals were subsequently used for the formulation of immediate-release (IR) matrix tablets.

Molar Masses:

- Candesartan cilexetil (MW) = 610.67 $g \cdot mol^{-1}$
- Hydrochlorothiazide (HCTZ, MW) = 297.74 $g \cdot mol^{-1}$
- Urea (MW) = 60.06 $g \cdot mol^{-1}$

Moles Corresponding to Tablet Dose (for Reference / Small Scale):

- Candesartan 16.00 mg → 2.62×10^{-5} mol
- HCTZ 12.50 mg → 4.20×10^{-5} mol
- Candesartan cilexetil: Urea — per tablet (API = 16.00 mg)

TABLE 3: MOLAR RATIO OF CANDESARTAN CILEXETIL CO CRYSTAL

Molar ration (API: Urea)	Urea moles (mol)	Urea mass (mg)	Urea total (mg)	% of 300mg tablet
1:1	2.6201×10^{-5}	1.5736mg	17.5736mg	5.86%
1:2	5.2401×10^{-5}	3.1472mg	19.1472mg	6.38%
1:3	7.8602×10^{-5}	4.7208mg	20.7208mg	6.91%

(Percent = (API + urea mass) / 300mg × 100) HCTZ: Urea — per tablet (API = 12.50 mg).

TABLE 4: MOLAR RATIO OF HYDROCHLOROTHIAZIDE COCRYSTAL

Molar ration (API: Urea)	Urea moles (mol)	Urea mass (mg)	API + Urea total (mg)	% of 300mg tablet
1:1	4.1983×10^{-5}	2.5215mg	15.0215mg	5.01%
1:2	8.3966×10^{-5}	5.0430mg	17.5430mg	5.85%
1:3	1.2595×10^{-4}	7.5645mg	20.0645mg	6.69%

Co-crystal Optimization and Tableting Screening and Selection: 6.69 % Conduct equilibrium solubility studies for all six co-crystal batches (Candesartan–Urea 1:1, 1:2, 1:3 and HCTZ–Urea 1:1, 1:2, 1:3) and compare with pure APIs in pH 6.8 phosphate buffer. Select the ratio showing maximum solubility enhancement for each drug as the optimized co- crystal.

Characterization of Optimized Co-crystals: Perform solid-state and dissolution characterization using:

PXRD: To confirm new crystalline phase formation.

FTIR: To identify intermolecular interactions.

***In-vitro* Dissolution Studies:** To assess dissolution improvement. Select the co crystals showing the highest solubility, dissolution rate, and confirmed new phase for tablet formulation.

Formulation of Immediate-Release (IR) Tablets: Prepare direct compression blends using the optimized co-crystals. For each drug, formulate two sub-batches with super disintegrant concentrations of 2.5% and 5%. The total tablet weight is 300 mg, based on the fixed-dose combination of Candesartan and HCTZ **Table 5.**

TABLE 5: COMPOSITION OF CO CRYSTAL MATRIX IR TABLET

Ingredient	Function	Quantity per 300mg Tablet
Candesartan-Urea Co-crystal	API	Asper dose (e.g., equivalent to 16 mg or 32mg of Candesartan)
HCTZ-UreaCo-crystal	API	As per dose (e.g., equivalent to 12.5 mg or 25mg of HCTZ)
Microcrystalline Cellulose (MCC)	Diluent/Binder	To make up the bulk
Hydroxypropyl Cellulose (HPC)	Binder	2-3% of total weight
Aerosil	Glidant	0.5-1% of total weight
Magnesium Stearate	Lubricant	0.5-1% of total weight
Superdisintegrant	Disintegrant	2.5% or 5% of total weight

To prepare the formulations, you'll need to scale up these quantities for your batch size (e.g., 100 or 1,000 tablets). Direct Compression Procedure: The same procedure was followed for all six batches, varying only in the type and concentration of super disintegrant.

Weighing and Sieving all ingredients (except magnesium stearate) were accurately weighed and passed through a #40 mesh sieve for uniform particle size.

Blending Co-crystals, MCC, and HPC were blended for 10–15 min, followed by addition of the respective super disintegrant (SSG, Crospovidone, or CCS at 2.5% or 5%) and mixed for 5 min. Aerosil was added and blended for 3–5 min, then magnesium stearate for 2–3 min to avoid over-lubrication.

Compression: The final blend was compressed using a rotary tablet press (9 mm punch) to obtain tablets of 300 mg with desired hardness.

Storage: Tablets from each batch were stored in labeled airtight containers for further evaluation.

Compression of IR Matrix Co-Crystal Tablet: The tablets were compressed using a Cadmach compression machine equipped with standard B-type tooling and a round, shallow concave punch of 9 mm diameter. Compression was performed at a speed of 20 rpm, applying a pressure of 6 kN. Each tablet had an average weight of 300 mg, a thickness of 4 mm, and a hardness of 5 kg/cm².

Pre-Compression Evaluation [22-23]: Pre-compression evaluation ensures that the powder have suitable flow, compressibility, and uniformity for direct compression. The following tests were performed [14, 15].

Angle of Repose: The angle of repose was measured to assess the flowability of the powder. It is defined as the maximum angle between the surface of a heap of powder and the horizontal plane, calculated using $\tan \theta = h/r$, where h is the height and r is the radius of the heap.

Bulk Density: Bulk density was determined as the mass of powder per unit volume before tapping. It indicates the packing efficiency of the powder blend.

Tapped Density: Tapped density was measured after mechanically tapping the powder to obtain the maximum packing density.

Carr's Compressibility Index & Hausner's Ratio: Carr's index was calculated from the bulk and tapped densities to evaluate the compressibility and flow characteristics of the granules. Hausner's ratio was determined as an indirect measure of inter-particle friction and flowability.

Post-Compression Evaluation [24-27]:

Tablet Thickness: The thickness of the IR matrix co crystal tablet was measured using a Vernier caliper to ensure uniformity across all batches.

Weight Variation: Twenty tablets were randomly selected from each batch and weighed individually. The average weight and standard deviation of the tablets were calculated to assess uniformity.

Hardness: The hardness of five tablets from each formulation was measured using a Monsanto hardness tester to determine the mechanical strength of the tablets.

Friability: Twenty tablets were weighed and placed in a Roche friabilator, which was rotated at 25 rpm for 4 minutes. After the test, tablets were dusted and reweighed. Friability was calculated as the percentage weight loss.

Disintegration Test: Disintegration of tablets for the Co Crystal IR tablet was carried out using a disintegration apparatus. Tablets were placed in 0.1 N HCl at 37 ± 0.5°C, and the time taken for complete disintegration of Co Crystal IR tablet was recorded.

Drug Content Uniformity: The assay of matrix IR Co Crystal tablet was performed using the validated simultaneous estimation method. Twenty tablets were weighed, powdered, and an amount equivalent to the label claim was dissolved, filtered, and suitably diluted. Absorbances were measured at 254 nm and 271 nm, and drug content was calculated using the simultaneous equations. Results were expressed as the percentage of the labelled amount for each drug.

***In-vitro* Dissolution Studies:** Dissolution studies were performed using a USP Type II (paddle) apparatus at 50 rpm and 37 ± 0.5°C in pH 6.8 phosphate buffer prepared with KH_2PO_4 and NaOH. Samples were withdrawn at 15, 30, 45, and 60 minutes, filtered, and analyzed spectrophotometrically at 254 nm and 271 nm. Percentage drug release was calculated, and the dissolution profiles were compared with pharmacopeial standards to evaluate performance.

Release Kinetics [28, 29]: The Hixson–Crowell cube root model was applied to the dissolution data of Candesartan–HCTZ co-crystal immediate-release tablets using the DD-Solver software to determine whether the drug release mechanism is governed by changes in surface area and particle diameter due to tablet disintegration and erosion. This model is particularly appropriate since both drugs exhibit low aqueous solubility, and their release from the co-crystal matrix involves a gradual reduction in particle size during dissolution.

Stability Studies [30]: The stability testing was conducted to provide evidence regarding the variation in quality of the Co Crystal Immediate Release (CCIR) over time under the influence of various environmental factors, including temperature, humidity, and light.

Stability studies were performed in accordance with ICH guidelines. The CCIR tablets were packaged in high-density polyethylene (HDPE) containers and stored under accelerated conditions at a temperature of 40°C ± 2°C and relative humidity (RH) of 75% ± 5% in a stability chamber. Samples were withdrawn at predetermined intervals and were evaluated for physical appearance, hardness, friability and drug content.

Chemical Compatibility Study:

FTIR Spectrophotometry Studies:

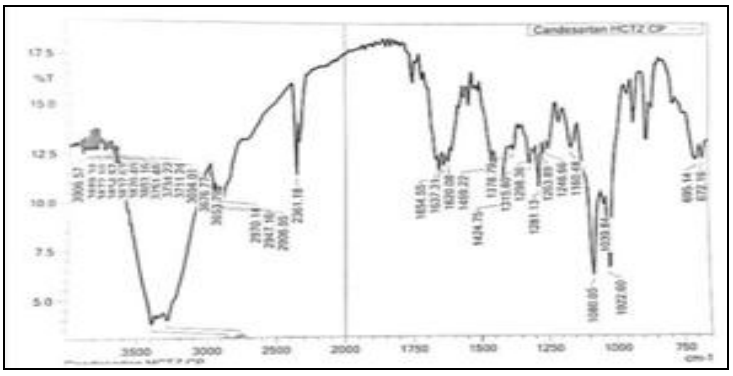

FIG. 3: FTIR SPECTRUM OF CANDESARTAN–HCTZ CO-CRYSTALBLEND WITH CROSPOVIDONE

FTIR analysis was performed to evaluate the chemical compatibility of Candesartan Cilexetil–Hydrochlorothiazide (CC–HCTZ) co-crystals with the superdisintegrant Crospovidone (CP). The characteristic absorption peaks of CC and HCTZ were retained in the co-crystal blend without significant shifts or disappearance **Fig. 4**, indicating preservation of drug identity. Minor peak broadening observed in the blend is attributed to intermolecular hydrogen bonding, suggesting physical interaction rather than chemical incompatibility. The absence of new peaks or major spectral changes confirms that the co-crystals are chemically stable and physically compatible with Crospovidone, supporting their suitability for tablet formulation Powder X-ray diffraction (PXRD)

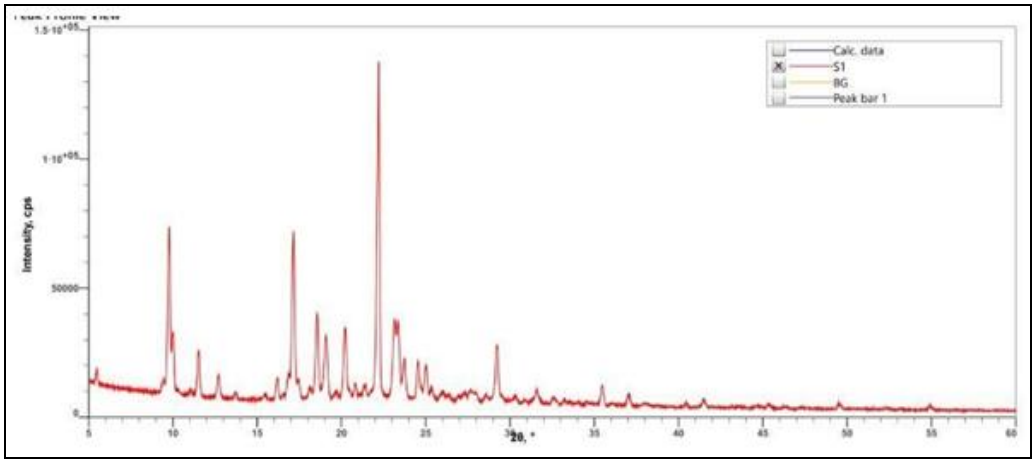

FIG. 4: PXRD PATTERN OF OPTIMIZED CANDESARTAN–UREA (1:2) CO-CRYSTAL

PXRD patterns of the Candesartan Cilexetil and Hydrochlorothiazide co-crystals showed the appearance of new diffraction peaks along with shifts and/or disappearance of characteristic API peaks **Fig. 4** and **5.** These changes confirm the formation of new crystalline phases, indicating successful co-crystallization rather than a simple physical mixture. The observed peak shifts suggest altered intermolecular interactions, likely due to hydrogen bonding between the drug and co-former, resulting in a modified crystal lattice. Overall, PXRD analysis provides clear evidence of distinct crystallographic structures for both Candesartan and HCTZ co-crystals.

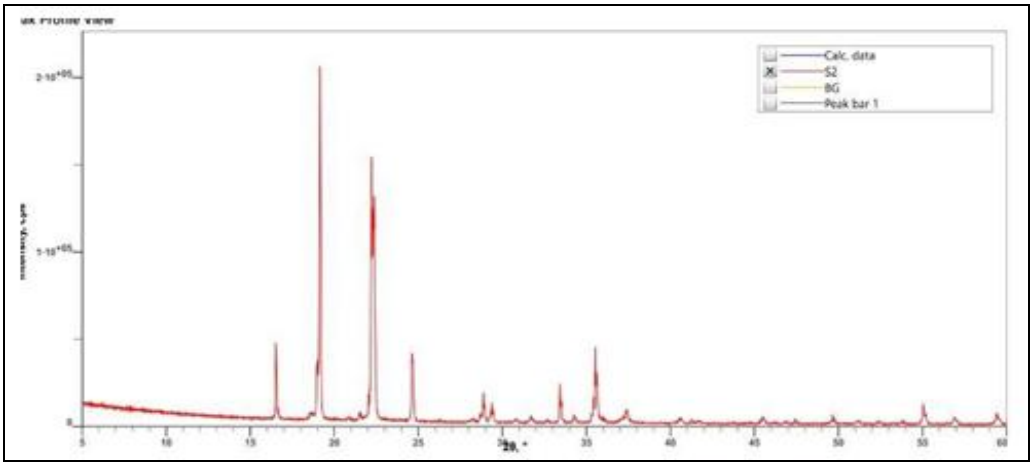

FIG. 5: PXRD PATTERN OF HYDROCHLOROTHIAZIDE CO CRYSTAL

Solubility Studies for Co-crystal: The solubility study revealed that co-crystallization with urea significantly enhanced the solubility of both drugs compared to their pure forms. Pure Candesartan Cilexetil showed a solubility of 1.8 µg/mL, which increased to 2.3 µg/mL for the 1:1 co-crystal, 6.2 µg/mL for the 1:2 co-crystal, and 5.1 µg/mL for the 1:3 co-crystal. Similarly, pure Hydrochlorothiazide exhibited a solubility of 0.71 mg/mL, which improved to 1.24 mg/mL (1:1), 2.49 mg/mL (1:2), and 1.53 mg/mL (1:3). Among these, the 1:2 (drug:urea) ratio for both Candesartan and HCTZ

demonstrated the highest solubility enhancement. This improvement is attributed to optimal hydrogen bonding between the drug molecules and urea, where urea effectively disrupts the strong drug–drug interactions in the crystal lattice and forms a more hydrophilic structure. The 1:1 ratio showed moderate enhancement, while the 1:3 ratio exhibited reduced solubility, likely due to steric hindrance or excess urea self-association. Therefore, the 1:2 molar ratio was selected as the optimal formulation for both drugs, and the resulting co-crystals were combined and compressed into a single matrix immediate-release tablet. The formulation table details the specific composition of a Matrix Immediate Release (IR) tablet, combining the drug co-crystals with a blend of excipients designed for rapid disintegration and drug release in **Table 6**.

TABLE 6: FORMULATION TABLE OF CANDESARTAN CILEXETIL - HCTZ CO - CRYSTAL MATRIX IR TABLET

S. no.	Ingredients		F1 MG	F2 MG	F3 MG	F4 MG	F5 MG	F6 MG
1	Candesartancilextil co-crystal		19.14	19.14	19.14	19.14	19.14	19.14
2	Hydrochlorothiazide co-crystal		17.54	17.54	17.54	17.54	17.54	17.54
3	Manito l100sd		100	100	100	100	100	100
4	Microcrystalline cellulose 102		140.82	133.32	140.82	133.32	140.82	133.32
5	Hydroxypropyl cellulose		9	9	9	9	9	9
6	Disintegrants	Cp	7.5	15	-	-	-	-
		CCS	-	-	7.5	15	-	-
		SSG					7.5	15
7	Magnesium stearate		3	3	3	3	3	3
8	Aerosil		3	3	3	3	3	3
	Total weight (mg)		300	300	300	300	300	300

Pre-Compression Studies:

TABLE 7: PRE-COMPRESSION PARAMETERS OF COCRYSTAL MATRIX IR TABLET

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner 's ratio	Carr's index (%)	Angle of repose (ɵ)	Flow property
F1	0.44	0.57	1.3	22.8	30	Fair
F2	0.48	0.56	1.33	20	31	Good
F3	0.48	0.6	1.25	20	28	Good
F4	0.42	0.56	1.33	25	31	Passable
F5	0.47	0.62	1.32	24.2	30	Fair
F6	0.43	0.58	1.35	25.9	32	Passable

*Mean± SD (n=3)

Pre-compression results for all formulations (F1–F6) presented in **Table 7** showed bulk density and tapped density values of 0.42–0.48 g/mL and 0.56–0.62 g/mL, respectively, indicating uniform packing and good blend homogeneity. Hausner's ratio (1.25–1.35) and Carr's index (20–25.9%) were within acceptable limits, confirming fair to good flow and compressibility. The angle of repose (28°–32°) further supported satisfactory flow properties essential for uniform die filling. Among the batches, F2 and F3 showed superior flow characteristics, indicating better handling and processability during compression.

Post-Compression Evaluation:

Physical Parameters:

TABLE 8: POST-COMPRESSION PARAMETERS OF MATRIX IR TABLET

Formulation Code	Appearance	Thickness (mm)	*Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Disintegration time (min)
F1	White, smooth, circular, flat	3.45	302.2	5.2	0.38	4.8
F2	White, smooth, circular, flat	3.48	304.2	5.6	0.31	4.2
F3	White, smooth, circular, flat	3.52	303.6	4.8	0.55	6.5
F4	White, smooth, circular, flat	3.4	306.8	6	0.3	5.5
F5	White, smooth, circular, flat	3.54	301.4	5.1	0.45	6
F6	White, smooth, circular, flat	3.4	304.8	6.2	0.25	4.9

*All the values are mean ± SD, n=10

Post-compression evaluation results **Table 8** showed that all formulations (F1–F6) produced white, smooth, circular, and flat tablets with uniform appearance and thickness (3.40–3.54 mm), confirming consistent die fill. Average tablet weights (301.4–306.8 mg) were within pharmacopeial limits (±5%). Hardness values (4.8–6.2 kg/cm²) indicated adequate mechanical strength, while friability (<1%) confirmed excellent durability. Disintegration times (4.2–6.5 min) met the requirements for immediate-release tablets (<15 min). Among all, F2 showed the shortest disintegration time (4.2 min) with optimal hardness (5.6 kg/cm²) and low friability (0.31%), demonstrating the best balance of strength and rapid disintegration.

Drug Content: All formulations (F1–F6) of Candesartan Cilexetil co-crystals and HCTZ co-crystals showed drug content within pharmacopeial limits (90–110%). Candesartan Cilexetil content ranged from 98.25% to 100.21%, while HCTZ content ranged from 98.21% to 99.96%, confirming uniform drug distribution and consistency in the co-crystal tablet formulation process.

***In-vitro* Dissolution Test of Co-Crystal Matrix IR Tablet:** *In-vitro* dissolution studies were carried out for all six formulations (F1–F6) to evaluate the drug release behavior of Candesartan cilexetil and Hydrochlorothiazide from the co-crystal matrix IR tablets. The cumulative percentage drug release at various time intervals is presented in **Table 9** (F1 F3) and **Table 10** (F4–F6). Among all formulations, F2 exhibited the most rapid and consistent drug release for both drugs, achieving more than 85% drug release within 30 minutes, thereby complying with the criteria for immediate-release dosage forms. The optimized formulation demonstrated a faster dissolution rate compared to other batches.

The dissolution profiles of the optimized formulation (F2) for Candesartan cilexetil is depicted in **Fig. 6.** The enhanced dissolution performance of formulation F2 can be attributed to co-crystallization with urea, which improves wettability, reduces crystal lattice energy, and facilitates faster drug diffusion into the dissolution medium.

TABLE 9: *IN-VITRO* DISSOLUTION PROFILE OF FORMULATIONS (F1–F3) CUMULATIVE PERCENTAGE DRUG RELEASE

Time	F1		F2		F3	
	CAN-CIL co-crystal	HCTZ co-crystal	CAN-CIL co-crystal	HCTZ co-crystal	CAN-CIL co-crystal	HCTZ co-crystal
0	0	0	0	0	0	0
5	11.36692	12.57506	13.77021	16.26236	9.093533	10.06005
10	34.29561	28.6836	36.87211	39.93395	31.32939	28.3164
15	50.01443	55.33025	53.82506	56.11732	49.23499	51.89654
20	77.20843	65.52887	78.13943	75.13025	77.25173	64.71963
30	86.79994	86.08268	91.90964	91.39261	83.76876	85.12933
45	95.50375	99.82587	99.35768	99.8037	94.98412	98.73672
60	98.21	99.998	100.2021	100.2236	100.7434	99.10808

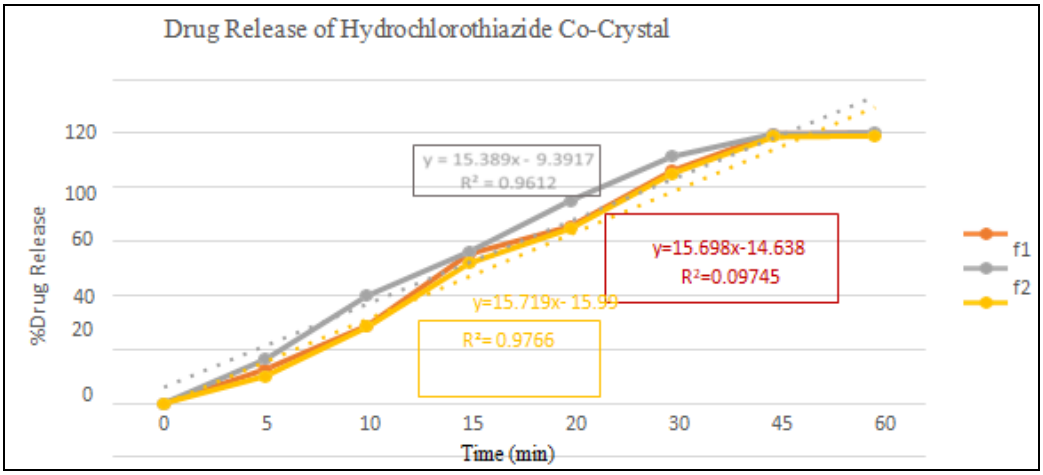

FIG. 6: *IN-VITRO* DISSOLUTION PROFILE OF CANDESARTAN CO-CRYSTAL IR TABLET (F2)

TABLE 10: *IN-VITRO* DISSOLUTION PROFILE OF FORMULATIONS (F4–F6) CUMULATIVE PERCENTAGE DRUG RELEASE

Time	F4		F5		F6	
	CAN-CIL co-crystal	HCTZ co-crystal	CAN-CIL co-crystal	HCTZ co-crystal	CAN-CIL co-crystal	HCTZ co-crystal
0	0	0	0	0	0	0
5	13.6836	7.080831	8.01097	12.29099	8.573903	12.5709
10	30.59324	38.47344	31.71911	28.23326	39.08054	27.46282
15	51.097	53.09931	51.097	53.09931	52.8291	56.72979
20	75.45468	64.103	76.92696	65.38891	78.05283	65.94873
30	83.68216	86.74781	84.82968	85.103	87.01645	85.63649
45	95.61201	99.60277	91.08689	99.56813	92.19111	98.73256
60	95.78522	99.96582	98.12356	99.46697	98.57823	99.96998

***In-vitro* Kinetic Studies:** The *in-vitro* drug release data of the optimized F2 immediate-release tablet formulation were subjected to mathematical modelling using the Hixson–Crowell cube-root equation to elucidate the drug release mechanism, and the corresponding plot was constructed to determine the release kinetics of the formulation in the **Fig. 7, 8.**

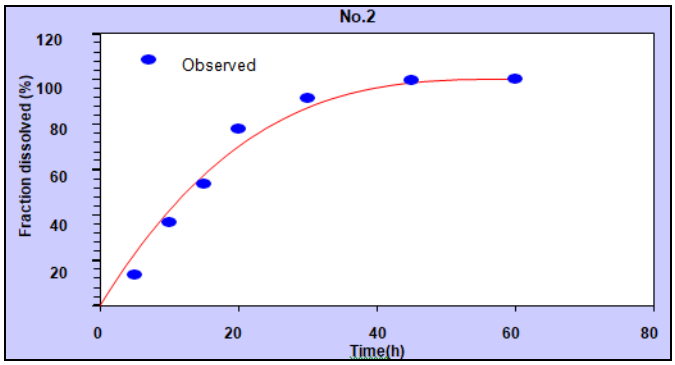

FIG. 7: A PLOT FOR HIXSON-CROWELL KINETICS FOR CAN - CIL CO – CRYSTAL

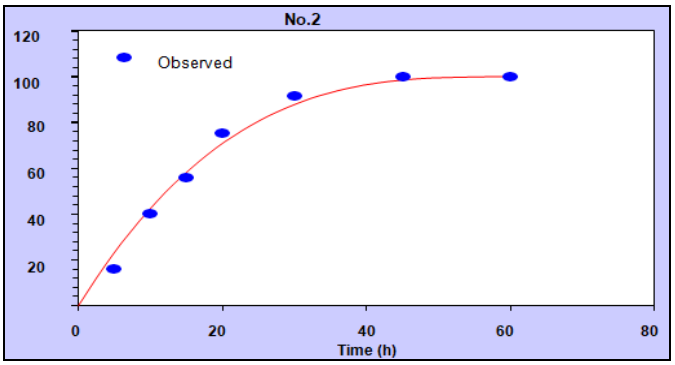

FIG. 8: A PLOT FOR HIXSON-CROWELL KINETICS FOR HCTZ CO - CRYSTAL

The *in-vitro* drug release data of the optimized F2 immediate-release (IR) tablet formulation containing Candesartan Cilexetil co-crystal and Hydrochlorothiazide co-crystal were analyzed using the Hixson–Crowell model by DD-Solver, which showed the best fit with R^2 values of 0.9854 for Candesartan Cilexetil and 0.9832 for Hydrochlorothiazide, indicating that the drug release from the formulation is governed by surface area reduction during dissolution.

Stability Studies: Stability studies were carried out for the optimized co crystal matrix IR tablet formulation in accordance with ICH guidelines to assess the effect of storage conditions on product quality. The formulation was stored under room temperature conditions and under accelerated conditions (40 °C / 75% RH) for a specified period. The evaluated parameters included physical appearance, hardness, friability, and drug content. Stability studies showed no significant changes in physical appearance, hardness, or friability under both storage conditions for 30 days. Hardness remained between 5.4–5.6 kg/cm², and friability stayed below 0.5%, confirming mechanical stability. Drug content for both candesartan and HCTZ remained above 99%, indicating chemical stability. Drug release profiles showed negligible variation, confirming excellent formulation stability under both room and accelerated conditions.

CONCLUSION: This study successfully developed immediate-release matrix tablets containing co-crystals of Candesartan Cilexetil and Hydrochlorothiazide using the direct compression technique. Co crystallization significantly enhanced the solubility and dissolution of both poorly water soluble drugs, enabling their effective incorporation into a single oral dosage form for hypertension management. Pre-compression and post-compression evaluations confirmed acceptable flow, compressibility, mechanical strength, and uniformity of the tablets.

Among the six formulations tested, F2 containing 5% Crospovidone demonstrated optimal performance, achieving rapid and complete drug release within 60 minutes. Dissolution data best fitted the Hixson–Crowell model, indicating surface area-dependent drug release. Stability studies conducted as per ICH guidelines showed no significant changes in physical properties or drug content, confirming formulation stability. Overall, the optimized co-crystal matrix tablet represents a promising and patient-friendly approach to improve oral bioavailability and therapeutic efficacy of antihypertensive combination therapy, warranting further *in-vivo* and pharmacokinetic evaluation.

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