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Dual-strategy; complexation-based solid dispersion for enhancing the solubility and dissolution rate of candesartan cilexetil

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Abstract

Background and objective: Candesartan cilexetil (CC), an angiotensin II receptor blocker indicated for hypertension and heart failure, is classified as a BCS Class II drug which is characterized by low aqueous solubility (0.963 ± 0.062 µg/mL) and limited oral bioavailability (14%–40%). Both factors significantly undermine its therapeutic efficacy and present challenges in formulation development. This study aimed to improve the solubility and dissolution properties of CC through two formulation techniques of solid dispersion with PVPK30 by rotavapor and inclusion complex with HPβCD by kneading.

Methods: In this study, solid dispersions and inclusion complexes were formulated at drug to polymer ratios of 1:1, 1:3, and 1:6, with corresponding physical mixtures at a 1:6 ratio. A study on saturated solubility was performed in distilled water. The best formulations—SD3 (solid dispersion with PVP K30) and IC3 (inclusion complex with HPβCD)—were subjected to further characterization. The characterizations consisting of percent drug content, in vitro drug release, Fourier Transform Infrared Spectroscopy, and Powder X-ray Diffraction were performed.

Results: SD3 and IC3 improved the solubility of CC by 21.19-fold (20.40 ± 0.139 µg/mL) and 12.22-fold (11.76 ± 0.202 µg/mL), respectively. Both exhibited high drug content—98.47% (SD3) and 98.21% (IC3)—and accomplished over 90% drug release within 15 minutes. FTIR confirmed hydrogen bonding and non-covalent interactions, however PXRD revealed diminished crystallinity and enhanced amorphization.

Conclusion: Both PVP K30-based solid dispersion via rotavapor and HPβCD-based inclusion complexation through kneading significantly improved the solubility and dissolution rate of Candesartan cilexetil, with solid dispersion demonstrating superior efficacy for enhancing oral bioavailability.

Keywords: Candesartan cilexetil, Solid dispersion, Inclusion complex, Hydroxypropyl β-Cyclodextrin, Polyvinylpyrrolidone K30.

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Introduction

Oral administration is the most commonly used route of drug delivery since it is non-invasive, self-administered, and is more acceptable to patients. But some drugs are hindered by poor bioavailability due to poor solubility, first-pass metabolism, and degradation in the stomach or by intestinal enzymes like CYP-3A4. Bioavailability is affected by numerous physiological and formulation considerations (1).

The Biopharmaceutics Classification System (BCS) categorizes drugs based on solubility and permeability. Class II drugs are poorly soluble but very permeable, so dissolution is most critical in improving efficacy. Class IV drugs are both poorly soluble and poorly permeable, which is more challenging for formulation and increases the time and cost of development (2).

Due to the limited absorption and bioavailability of poorly soluble medications, enhancing their solubility and/or dissolution rate is essential. A number of various methods have been proposed to enhance the solubility of poorly soluble pharmaceuticals (3). Some of those methods involve size reduction, dendrimers, salt formation, co-solvency, complexation with cyclodextrin, pH modification, self-emulsifying drug delivery system, and solid dispersion systems (4, 5). Each strategy has unique benefits and drawbacks. Among the various techniques available, the solid dispersion approach is particularly significant. It is defined as the dispersion of one or more active pharmaceutical ingredients within a hydrophilic inert carrier or matrix in the solid state, typically prepared using methods such as fusion, kneading, or solvent evaporation. It transforms the particles into an amorphous state and decreases particle size, hence enhancing the wettability, porosity, and solubility of the drug particles. Solid dispersion strategies enhance medication stability through minimizing particle agglomeration and may be utilized to control and extend medication release (6).

Polyvinylpyrrolidone (PVP) is the most widely employed hydrophilic and amorphous polymer. They enhance water uptakeand stabilize the drug in the amorphous state from recrystallization by forming a hydrophilic matrix. It is commonly used for film formation, solubilization, stabilization, taste masking, and maintaining supersaturation, ultimately improving drug solubility and dissolution (7).

Another way of enhancing solubility is the inclusion complexation with β-cyclodextrin (β-CD) or its derivatives, which increases the solubility,

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bioavailability and efficacy of poorly water-soluble drugs (8). The mechanism is the removal of water molecules from the cyclodextrin cavity so that the drug molecule can enter the cavity through hydrogen bonding, hydrophobic interaction, and van der Waals interaction. Hydroxypropyl-β-cyclodextrin (HP-β-CD) also improves solubility and prevents drug crystallization during storage, maintaining dissolution properties. Hydroxypropyl β-cyclodextrin offers better solubility and complexation than β-cyclodextrin (9).

Candesartan cilexetil (CC) is an ester prodrug used to treat hypertension and heart failure, either alone or with other therapies like ACE inhibitors or diuretics. After oral administration, CC is converted to its active form, candesartan, an angiotensin II receptor blocker with antihypertensive effects. Despite its benefits, CC is a BCS Class II drug with low solubility and variable oral bioavailability (15–40%) due to poor absorption and first-pass metabolism (10). Increasing its water solubility could enhance its absorption and its therapeutic effect. Its bioavailability is about 40% when in solution form and 14% in tablet form, with peak plasma levels reached in 3–4 hours after oral dosing (11).

The aim of this study is to enhance the solubility and bioavailability of poorly water-soluble BCS Class II drug candesartan cilexetil by two formulation methods:(1) Preparation of solid dispersions with polyvinylpyrrolidone K30 (PVP K30) utilizing the solvent evaporation technique via a rotary evaporator, and (2) Preparation of an inclusion complex with hydroxypropyl beta-cyclodextrin (HP-β-CD) through the kneading method.

Materials and Methods

Design, setting, and time of study

This experimental research study was carried out in the College of Pharmacy, Hawler Medical University, from 1st of November 2024 to 1st of May 2025.

Materials

CC was kindly gifted from Awamedica Pharmaceutical Company (Erbil, Iraq). PVP K30 were procured from Simson Pharma (Mumbai. India), and HPβCD were supplied by Sigma Pharma (China). All other chemical substances and solvents used were of all analytical grades.

Determination of CC maximum absorbance (λ max) and calibration curve

A standard stock solution of 100 µg/mL candesartan cilexetil (CC) was prepared by dissolving 10 mg in 100 mL of methanol. The solution was then analyzed for wavelength determination by UV-Visible (UV-1900, Shimadzu, Japan) double beam spectrophotometer within the 200-400 nm range, employing methanol as the blank to

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identify λ max. The calibration curve was established utilizing Beer's law through the dilution of the stock solution with methanol, yielding standard working solutions with concentrations of 2-28 µg/mL. The absorbance of the solutions was assessed at 254 nm. A calibration curve was generated in triplicate by plotting concentration against absorbance in order to ensure reproducibility (10, 12).

Preparation of Inclusion Complex by Kneading Method (IC1-IC3)

Candesartan cilexetil inclusion complexes with HP-β-CD were created by kneading at 1:1, 1:3, and 1:6 (w/w) drug-to-polymer ratios. Loading HP-β-CD into a mortar, a 1:1 v/v ethanol-water combination was gradually added to wet the polymer. After adding candesartan cilexetil, the mixture was kneaded for an hour to form a paste. After drying in the oven at 50 °C for 24 hours, the paste was crushed and passed through #70 mesh. For further examination, the complexes were preserved in airtight containers in desiccator (13). Each ratio prepared in triplicate.

Preparation of Solid Dispersion by Solvent Evaporation (SD1-SD3)

By solvent evaporation, candesartan cilexetil and PVP K30 solid dispersions were made in 1:1, 1:3, and 1:6 (w/w) ratios. Candesartan cilexetil was dissolved in methanol, then PVP K30 was added with constant agitation to make a transparent solution. To obtain a dry solid, the solvent was evaporated using a rotary evaporator (Rotavapor RE111, Büchi, Switzerland) under reduced pressure at 45°C water bath (B-480, Büchi, Switzerland) and maintained in a hot air-drying oven at 40±2°C for 24 hours. Pulverized dry matter was filtered through a #70 mesh filter and stored in a desiccator inside an airtight container for further investigation (3, 9). Each ratio was prepared in triplicate.

Preparation of Physical Mixtures (PM)

A drug: polymer ratio of 1:6 was employed for both solid dispersion and inclusion complex. The components are combined in a glass mortar and pestle for ten minutes to achieve homogeneity, thereafter sieved through a #70 mesh and stored in a desiccator, protected from light and humidity, until further assessment (14).

Saturated Solubility Study of Solid Dispersions (SDs), Inclusion Complex (IC) and Physical Mixture (PM) in Distilled Water

Saturation solubility tests were conducted to determine solubility of pure candesartan cilexetil, solid dispersions, inclusion complexes, and physical mixes in distilled water. The saturation solubility tests were conducted in triplicate using the method developed by Higuchi and Connors. An excess of solid dispersions, inclusion complexes, and physical

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mixtures were introduced into vials holding 10 ml of distilled water. The vials were agitated at 37±0.5°C for 24 hours using a mechanical isothermal bath shaker (SBS30, Stuart, UK) and subsequently allowed to remain undisturbed for a further 24 hours until equilibrium was attained. The pharmaceutical solutions were subjected to filtration via a 0.45µm grade syringe filter (Thermo Scientific, China). The filtrate was accurately diluted with the appropriate reagent, and the dilution was analyzed using a UV-visible double-beam spectrophotometer (3).

The enhancement ratios were found by the following formula: (15)

$$\text{Solubility Enhancement Ratio (SER)} = \frac{\text{Solubility of CC in SD or IC}}{\text{Solubility of CC in distilled water}} \quad \text{..... (Eq : 1)}$$

Characterization of Inclusion complex and solid dispersion

Determination of Percent Drug Content

The developed solid dispersion (SDRE) of candesartan cilexetil with PVP K30 (1:6) and inclusion complex (ICKN) of candesartan cilexetil with hydroxypropyl β-cyclodextrin (1:6) and their physical mixtures (PM) equivalent to 8 mg of candesartan cilexetil were accurately weighed and dissolved in 100 mL of methanol in a 100 mL volumetric flask to produce a stock solution of 100 µg/mL. The solutions were sonicated for 30 minutes until dissolved completely, then filtered through a 0.45 µm syringe filter. Dilutions were made as required using methanol as the solvent, and the drug content was determined with a UV-Visible double-beam spectrophotometer at 254 nm using methanol as the reference (16). Triplicate analysis was carried out on each sample. The average drug content ± standard deviation (SD) was calculated by the following formula: (12).

$$\text{Percentage drug content (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \text{X100} \quad \text{..... (Eq: 2)}$$

Determination of Percentage Drug Yield

The production yield (%) was determined by dividing the final weight of resultant solid dispersion and inclusion complex by the initial total weight of the drug and polymer (9). By using the following formula: (16)

$$\text{Percentage yield} = \frac{\text{actual weight}}{\text{theoretical weight of drug and carrier}} \text{X100} \quad \text{..(Eq : 3)}$$

In – Vitro Drug Release Study

Samples of selected complex (SDRE, ICKN, their physical mixtures), each accurately weighed by an analytical balance (Mettler Toledo) to 8 mg of CC and prepared using various methods, were placed in a USP type II (TDT-08L, Electrolab, India) dissolution apparatus. This study utilized a dissolution medium consisting of 900 mL of phosphate buffer solution at pH 6.5, supplemented

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with 0.35% Tween 20. The stirring rate was held constant at 50 ± 2 rpm, and the temperature was regulated at 37 ± 0.5°C. At designated time intervals of 5,10, 15, 30, 45 and 60minutes, 10 mL samples were collected and filtered using a 0.45-mm syringe filter. Subsequently, 10 mL of fresh dissolution fluid was added to the dissolution medium to ensure a consistent volume. The samples were spectrophotometrically examined at 254 nm, and the drug release was determined as the average of three measurements. The drug dissolution profile was represented as the percentage of drug release over time (16, 17). The results are presented in Table 3, and the subsequent equation was employed: (18)

$$\text{Percentage of Drug Release} = \frac{\text{Practical Drug Content}}{\text{Theoritical Drug Content}} \times 100 \quad \ldots\ldots \text{(Eq: 4)}$$

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were obtained using a Fourier Transform Infrared Spectrophotometer (FT/IR-4600, JASCO) to examine potential interactions between candesartan cilexetil and the carriers employed in the formulations. The spectra were acquired by preparing KBr discs that included 2 mg of the sample mixed with 200 mg of dry potassium bromide (KBr). Measurements were conducted across a scanning range of 400–4000 cm^{-1}, utilizing a resolution of 4 cm^{-1}. The resulting solid dispersion by rotavapor (SDRE), inclusion complex by kneading (ICKN), physical mixtures, pure CC, PVPK30, Hβ CD were among the seven samples analyzed (16).

Powder X-Ray Diffraction (PXRD) Studies

The Powder X-ray diffraction (PXRD) patterns of pure candesartan cilexetil, its inclusion complex with hydroxypropyl beta-cyclodextrin, and solid dispersion with PVP K30, prepared through rotary evaporation, were acquired using X'Pert PRO diffractometer (PANalytical, Netherlands) with Cu Kα radiation (λ = 1.5406Å), operating at 40 kV and 50 mA. Samples were evenly placed on the graticule and subjected to compression for stability. The collected data ranged from 5° to 70° 2θ, with a step increment of 0.01° and a length of 0.2 seconds each step, intended to ascertain the crystalline or amorphous properties of the formulations (19).

Statistical data analysis

All values were expressed as the mean of three replicates ± standard deviation (SD), and all experiments were performed in triplicate. Statistical analysis was conducted using GraphPad Prism version 10, employing both independent two-sample t-tests and one-way ANOVA which was then used to compare the dissolution release profiles of resulting solid dispersions,

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inclusion complexes and physical mixtures with pure medication. The difference was considered statistically significant when the value of P was less than 0.05; conversely, it was not considered significant when it exceeded 0.05.

Results

Determination of CC maximum absorbance (λ max) of candesartan cilexetil (CC)

The wavelength corresponding to maximum absorbance (λ max) was determined to be 254 nm in methanol with a correlation coefficient of 0.9994 for the linear regression equation.

Saturated Solubility Study of Solid Dispersions (SDs), Inclusion Complex (IC) and Physical Mixtures (PM) in Distilled Water

Two batches of binary formulations of candesartan cilexetil (CC) were created to enhance its solubility in water. In the initially produced batch, solid dispersions containing PVP K30 at drug-to-polymer ratios of 1:1, 1:3, and 1:6 were created via solvent evaporation and designated as SD1–SD3. In the second batch, inclusion complexes with HP-β-CD were synthesized using the kneading method in identical ratios and designated as IC1–IC3, with each ratio prepared in triplicate. The solubility equilibrium of CC in all compositions (Table 1) demonstrated an increase in response to polymer concentration.

Table 1. Saturation solubility of CC in different formulations

Formulation	Drug Ratio (SER) in Folds	Carrier Solubility (µg/mL)	Solubility Enhancement	P-value
CC	-	0.963 ± 0.062	--	<0.0001
SD1	1:1	3.711± 0.188	3.85	<0.0001
SD2	1:3	8.602 ± 0.188	8.94	<0.0001
SD3	1:6	20.40 ± 0.1392	1.19	<0.0001
IC1	1:1	1.936 ± 0.065	2.01	<0.0001
IC2	1:3	5.145 ± 0.036	5.34	<0.0001
IC3	1:6	11.76± 0.202	12.22	<0.0001
PMPVPK30	1:6	6.998 ± 0.078	7.27	<0.0001
PMHPβCD	1:6	8.934 ±0.078	9.28	

The Mean of three values ± Standard Deviation.

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Characterization of Inclusion complex and solid dispersion

Characterization was conducted only on the best formulations chosen from the solubility analysis. These were SD3 (1:6, rotary evaporation) and IC3 (1:6, kneading). Both exhibited the greatest solubility and were hence selected for additional analysis. Henceforth, the two formulas will be referred to as SDRE and ICKN for convenience.

Determination of Percent Drug Content

The assessment of drug content was performed exclusively on the improved formulations (SDRE and ICKN), which exhibited the greatest gain in solubility. The Percentage drug content data for both prepared formulations and their respective physical mixtures are presented in Table 2.

Table 2. Percentage of CC content in the solid dispersion prepared by solvent evaporation using rotavapor (SDRE), inclusion complex prepared by kneading (ICKN) and physical mixtures

Formulations	Method of Preparation	% Drug Content
SDRE	SE	98.47 ± 0.448
PMPVPK3	Blending	71.30 ± 0.593
ICKN	KN	98.21 ± 0.776
PMHPβCD	Blending	82.56 ± 0.977

The Mean of three values ± Standard Deviation.

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In – Vitro Drug Release Study

Table 3 displays the cumulative percentages of drug release for these formulations at six specified time intervals, whereas Figure 1 offers a visual comparison of their drug release profiles.

Table 3. The cumulative percentages of drug release for these formulations at six specified time intervals

Time (min)	CC	PMHPβCD	PMPVPK30	SDRE	ICKN
5	15 ± 0.100	47.1 ± 0.854	45.43 ± 1.320	87.23 ± 0.666	89.37 ± 1.31
10	29.6 ± 0.076	57.2 ± 0.666	56.67 ± 1.193	90.8 ± 0.814	90.07 ± 0.208
15	31.0 ± 0.144	69.5 ± 0.666	61.67 ± 0.71	92.4 ± 0.351	97.33 ± 0.723
30	35.0 ± 0.056	72.1 ± 0.794	65.57 ± 0.473	95.4 ± 0.436	98.23 ± 0.252
45	35.3 ± 0.245	74.8 ± 0.757	69.43 ± 1.320	98.67 ±0.306	100.7 ± 1.01
60	34.7 ± 0.204	82 ± 0.757	± 1.277	96.37 ± 0.289	99.2 ± 0.361
P-value	-	<0.0001	<0.0001	<0.0001	<0.0001

The Mean of three values ± Standard Deviation.

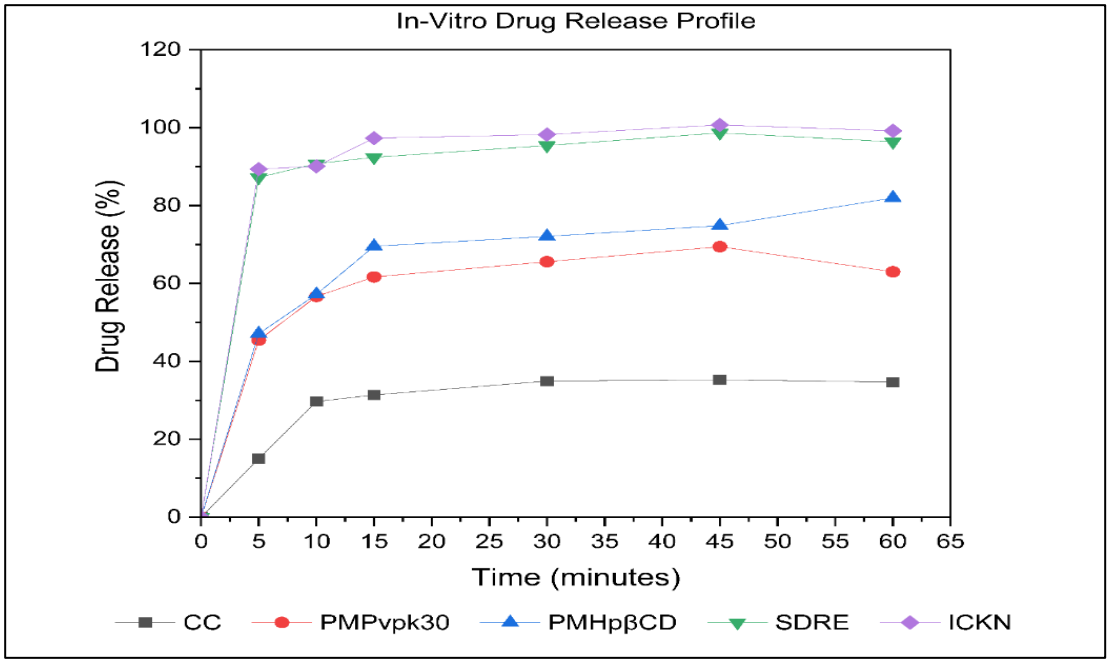

Figure 1. Comparison of the in vitro drug release profiles of pure candesartan cilexetil (CC), candesartan solid dispersion prepared by a rotary evaporator (SDRE), candesartan inclusion Complex prepared by kneading (ICKN), candesartan physical mixture with HpβCD (PMHPβCD) and candesartan physical mixture with PVPK30 (PMPVPk30)

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Fourier Transform Infrared Spectroscopy (FTIR)

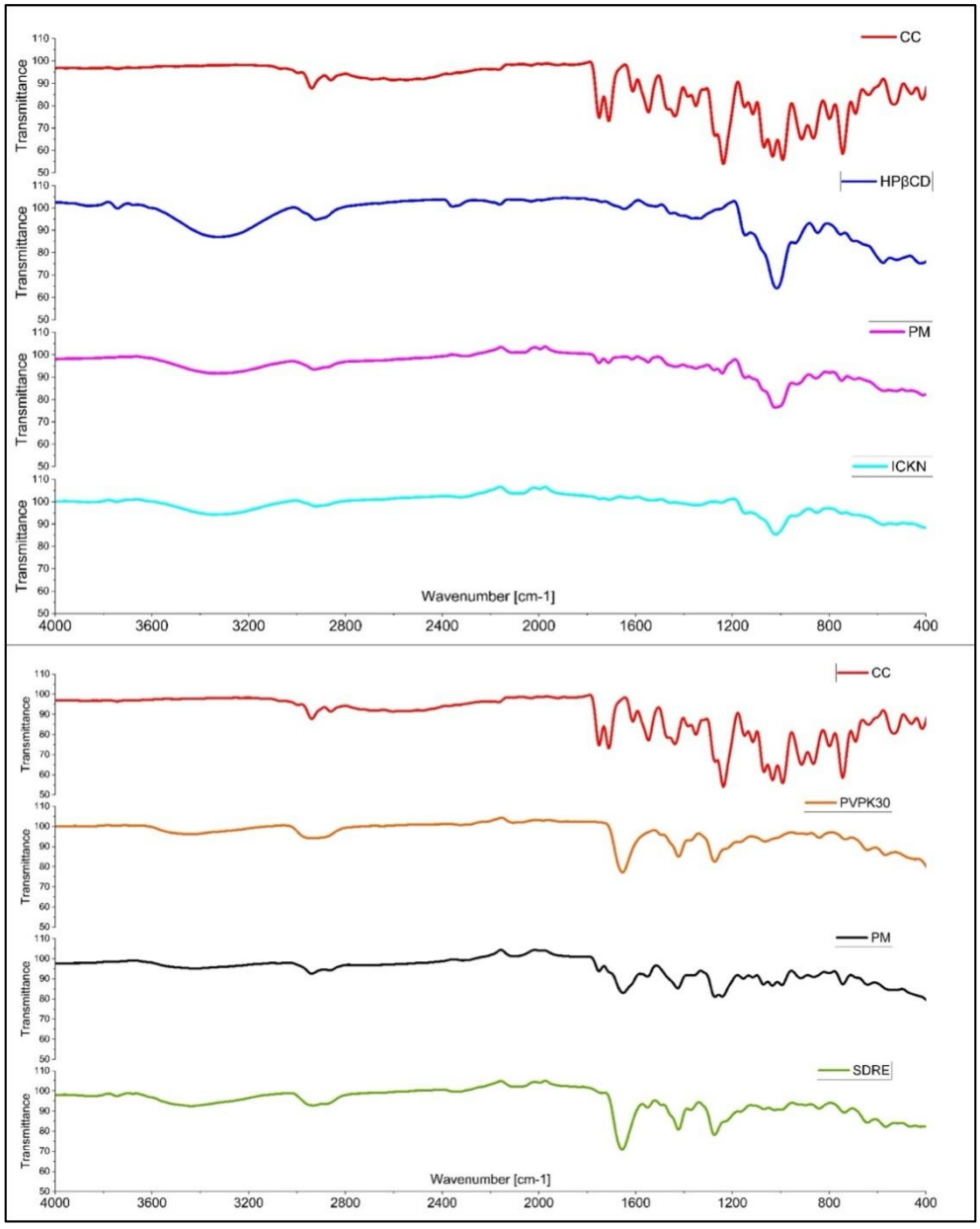

Figure 2. Fourier-transform infrared (FTIR) spectroscopy spectrum of pure candesartan cilexetil (CC), hydroxypropyl β-cyclodextrin (HPβCD), polyvinylpyrrolidone K30 (PVP K30), physical mixture of CC and HPβCD in a 1:6 ratio (PM in purple) , physical mixture of CC and PVP K30 in a 1:6 ratio (PM in black), solid dispersion of CC with PVP K30 in a 1:6 ratio prepared by rotary evaporator (SDRE), and inclusion complex of CC with HPβCD in a 1:6 ratio prepared by kneading method (ICKN)

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Powder X-Ray Diffraction (PXRD) Studies

The X-ray diffraction (XRD) patterns of pure Candesartan Cilexetil (CC), its solid dispersion with polyvinylpyrrolidone K30 prepared by rotary evaporation (SDRE), and its inclusion complex with hydroxypropyl β-cyclodextrin prepared by kneading (ICKN) are shown in Figure 3.

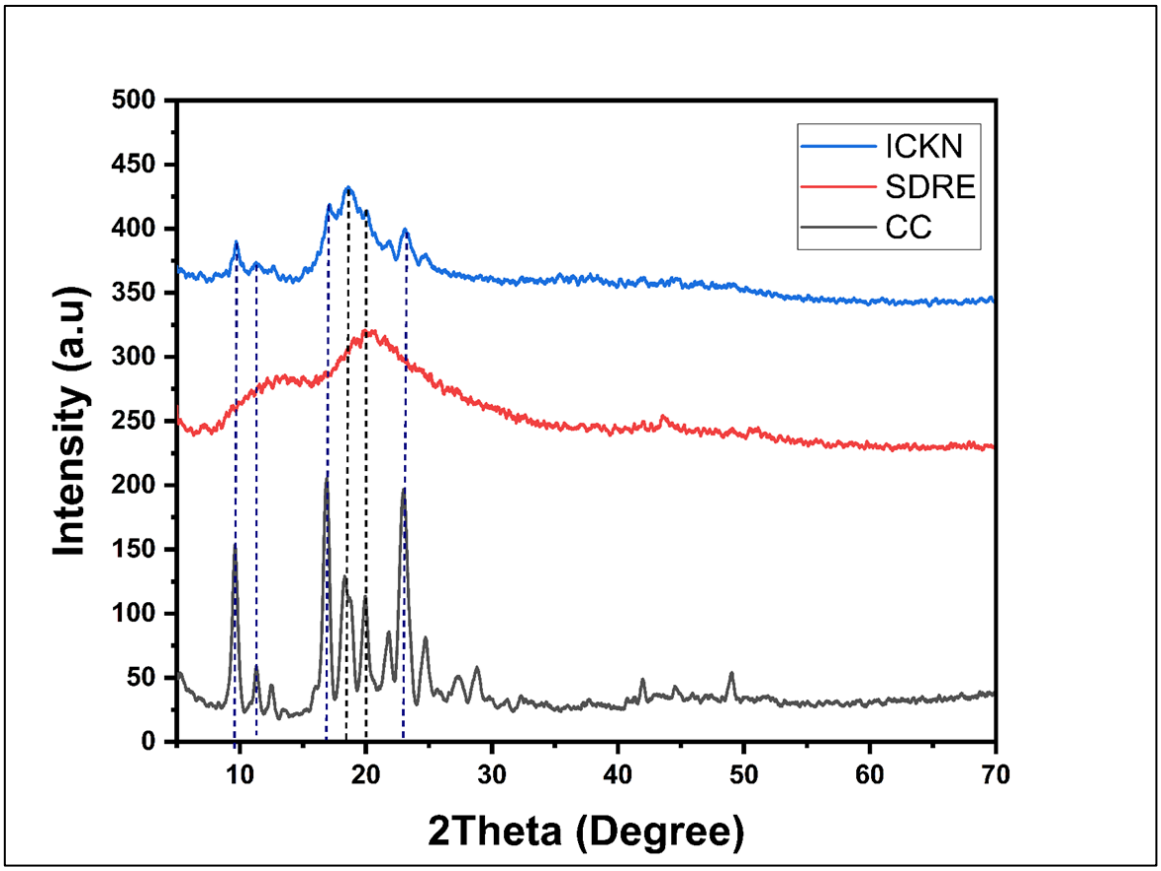

Figure 3. A comparative X-ray diffractogram of pure candesartan cilexetil (CC),candesartan solid dispersions (SDRE) and candesartan inclusion complex (ICKN)

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Discussion

Saturated Solubility Study of Solid Dispersions (SDs), Inclusion Complex (IC) and Physical Mixture (PM) in Distill Water

The solubility of the active pharmaceutical ingredient is a critical physicochemical property influencing many stages of drug research and development. Inadequate therapeutic response results from a drug's low aqueous solubility (20). The solubility and dissolution characteristics of CC were determined by quantifying its solubility within distilled water. The saturation solubility of pure candesartan cilexetil (CC) in distilled water was determined to be 0.963 ± 0.062 µg/mL, thereby confirming its limited aqueous solubility and categorization as a BCS Class II drug. The reported value aligns closely with the findings of Poudel and Kim, who documented a solubility of 1.03 ± 0.06 µg/mL for CC in deionized water under comparable experimental conditions (10).

The limited solubility of Candesartan cilexetil (CC), a BCS Class II medication, poses a considerable challenge to its oral bioavailability, requiring innovative formulation strategies to improve its solubility and therapeutic efficacy. Among the established systems, solid dispersions (SDs) utilizing polyvinylpyrrolidone K30 (PVP K30) via solvent evaporation demonstrated the greatest degree of solubility augmentation. A distinct trend dependent on polymer concentration was observed, with SD3 (1:6 drug-to-polymer ratio) exhibiting a solubility of 20.40 ± 0.139 µg/mL, indicating a 21.19-fold increase in solubility relative to pure CC (0.963 ± 0.062 µg/mL). Subsequently, SD2 (1:3, 8.602 ± 0.188µg/mL; 8.94-fold) and SD1 (1:1, 3.711 ± 0.188 µg/mL; 3.85-fold) were identified, confirming a direct correlation between polymer concentration and solubility enhancement. The enhancements result from several physicochemical phenomena, including the amorphization of CC, hydrogen bonding interactions, increased wettability, and molecular-level dispersion within the hydrophilic PVP matrix, which collectively reduce crystallinity and augment the available surface area for solvation (21).

Concurrently, inclusion complexes (ICs) formed by kneading CC with hydroxypropyl-β-cyclodextrin (HPβCD) also markedly enhanced drug solubility, although to a lower extent. A comparable trend based on carrier ratio was noted, with IC3 (1:6) measured at 11.76 ± 0.202 µg/mL, or a 12.22-fold increase. IC2 and IC1 exhibited solubilities of 5.145 µg/mL and 1.936 µg/mL, respectively. The results support the idea that the hydrophobic CC molecule is non-covalently encapsulated within the HPβCD cavity, which improves its

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aqueous dispersibility by means of host-guest association (22, 23). A local investigation at the University of Basrah (2023) unexpectedly revealed a 24.4-fold increase, demonstrating the capability of cyclodextrin-based carriers to improve the solubility of weakly water-soluble active pharmaceutical ingredients (APIs) (24). In contrast, physical mixtures of CC with PVP K30 and HPβCD exhibited negligible improvements in solubility. The PVP-based physical mixture (PMPVPK30) exhibited a solubility of 6.998 µg/mL, representing a 7.27-fold increase, whereas the HPβCD-based mixture (PMHPβCD) demonstrated a solubility of 8.934 µg/mL, indicating a 9.28-fold increase. The relatively modest enhancements are likely attributable to insufficient drug–carrier interactions or the absence of necessary structural modifications for extensive solubilization. Although statistically significant ($P < 0.0001$), these formulations demonstrate the relative disadvantage of simple mixing methods in comparison to more mechanically intensive procedures (25).

The established hierarchy of solubility enhancement (SD > IC > PM) is corroborated by comparative literature. This aligns with previous findings, including an 18.77-fold enhancement in CC solubility utilizing spray-dried PVP-based solid dispersions and a 21.19-fold increase with analogous systems (10). Kneaded inclusion complexes based on HPβCD have demonstrated substantial enhancements, with solubility increases of 6.58-fold for fenofibrate and over 10-fold for dexibuprofen (22, 23). Solvent-evaporated HPβCD complexes enhanced the solubility of norfloxacin by a factor of 27.95 compared to kneading and trituration. The results indicate that solvent-mediated solid dispersions are more efficacious and reproducible, particularly when employing hydrophilic carriers such as PVP K30. They also acknowledge the role of cyclodextrin inclusion (13). The statistically significant increases in solubility ($P < 0.0001$) across all treated formulations underscore the critical importance of drug–carrier interactions, preparation methods, and polymer ratios. They demonstrate that solvent evaporation and cyclodextrin-based methodologies may enhance the bioavailability of poorly soluble medicines such as CC.

Characterization of Inclusion Complex and Solid Dispersion

Determination of Percentage Drug Content and Yield

The percentage of drug content and yield of the manufactured products were analyzed to evaluate the efficacy of the preparation processes and the uniformity of drug integration inside the carriers. The solid dispersion produced via rotary evaporation with PVP K30 (SDRE) exhibited a drug content of 98.47 ± 0.448, while the inclusion

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complex formed through kneading with hydroxypropyl β-cyclodextrin (ICKN) yielded a comparable value of 98.21 ± 0. 776. The statistics confirm that all formulations adhere to expected drug content ranges, hence ensuring process dependability, preserving therapeutic levels, and minimizing side effects (26). The findings validate that both solvent evaporation and kneading methods successfully contained candesartan cilexetil (CC) within their respective matrices, according to specific pharmacopeial acceptability criteria of 90%–110%. Physical mixtures demonstrated reduced drug content—82.56 ± 0.977% (PMHPβCD) and 71.30 ± 0.593% (PMPVPK30)—due to insufficient molecular interactions, phase separation, and mixing inefficiencies. These factors contribute to uneven distribution and reduced bioavailability (27).

The ICKN yielded a higher output (91.10 ± 0.289%) compared to SDRE (86.64 ± 0.607%), likely attributable to the low-solvent and less complex kneading method. Rotary evaporation typically experiences material losses to glassware, solvent bumping, and scraping inefficiencies—characteristic disadvantages associated with solvent operation (10). The presence of clinging polymer-drug solutions and leftover solvents in SDRE would impede complete recovery (24). Rotary evaporators are restricted to the processing of one sample at one time, which poses a considerable challenge. The outcome of solid dispersion may remain in the rotary flask, resulting in limited extraction of the formulation from the flask (3). The kneading technique addresses these drawbacks, resulting in enhanced process efficiency and material retention, especially when HPβCD is utilized as a hydrophilic carrier (9).

In – Vitro Drug Release Study

Dissolution testing was done to make sure that after an oral administration, a given amount of the drug product will be released at a specified time (27). The dissolving profile of Candesartan Cilexetil (CC) varied significantly among formulations—pure drug, physical mixes (PVP K30 and HPβCD), solid dispersion (SDRE), and inclusion complex (ICKN)—demonstrating the impact of the formulation strategy on solubility enhancement. Figure (2) illustrates that ICKN and SDRE exhibited over 90% drug release at the 5-minute mark, which can be ascribed to improved wettability, augmented surface area in contact with the dissolution medium, and molecular dispersion of the drug inside hydrophilic matrices. The results correspond with Poudel and Kim, who noted a more than ninefold increase in the dissolving rate of CC utilizing PVPK30-based amorphous solid dispersions produced via spray drying. This enhancement was attributed to both the amorphous transformation and the supersaturation

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stability effect of the polymeric matrix utilized in the spray dryer (10). At 15 minutes, SDRE and ICKN showed nearly complete release (~98–99%), significantly exceeding the physical mixtures (PMHPβCD and PMPPVP30), which exhibited less than 70% release. The improved effectiveness of these novel formulations is due to the conversion of the drug into the less crystalline or amorphous state, as well as potential hydrogen bonding between the carrier and the drug, as indicated by FTIR and XRD analyses. The interactions interfere with the crystal lattice, promoting dissolution and preventing recrystallization during the dissolution process (9). Values were analyzed using an unpaired t-test; the two-tailed P value is less than 0.0001 when comparing pure CC and SDRE, with release rates of 92.4 ± 0.351 % for SDRE and 31.0 ± 0.144 %for pure CC. Similarly, ICKN exhibited a statistically significant increase (P <0.0001) when compared to the pure medication.

The longer release of ICKN is due to HPβCD's water-soluble nature and ability to stabilize non-covalent host-guest complexes with hydrophobic drugs. According to Aly et al. (2020), HPβCD is more stable and efficient when coupled with CC than βCD due to its greater water solubility and hydrogen bonding capacity of its hydroxypropyl groups (9). ICKN and SDRE maintained a stable plateau (>99%) during the 30–60-minute dissolution period, demonstrating consistent solubilization and effective drug-carrier interaction. ICKN's excellent performance was corroborated by Aziz and Al-Khedairy (2024), who found that CC inclusion complexes with HPβCD and hydrophilic polymers significantly enhanced solubility and drug release within 45 minutes. XRD measurements show amorphous nature and effective inclusion (24).

The physical mixtures exhibited limited enhancement; nonetheless, PMHPβCD displayed superior efficacy (~75–80%) compared to the physical mixture with PVP K30 (PMPVP30, ~63%). The statistical validation employing an unpaired two-tailed Student's t-test revealed a significant difference between the two physical mixtures and the pure CC, with $p < 0.0001$. However, the level of enhancement was lower than that achieved by the SDRE and ICKN formulations. The improved performance of PMHPβCD is due to the formation of partial complexes and the enhanced wettability provided by HPβCD, even in the absence of complete complexation (16). This result aligns with previous research on other poorly soluble drugs, such as norfloxacin where HPβCD-based inclusion complexes demonstrated significantly enhanced solubility and dissolution rates compared to their physical mixtures and the pure drug (13, 23).

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The dissolution of pure CC at 34.7 ± 0.204 within 60 minutes demonstrates its inherent solubility limitations characteristic of a BCS Class II drug. Research demonstrates that, without solubility enhancement techniques, CC shows limited oral bioavailability and insufficient aqueous solubility. The results demonstrate that solid dispersion and inclusion complexation improve the solubility and pharmacokinetics of poorly water-soluble drugs like CC. (24).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of drug-polymer formed systems generally exhibit peak shifts relative to physical mixtures, signifying specific interactions—usually hydrogen bonding, but perhaps ionic or hydrophobic—between drug and polymer functional groups. Modifications in the intensity or nature of these interactions may result in observable alterations in peak locations or amplitudes (28).

The FTIR spectrum of pure Candesartan cilexetil (CC) displayed distinct absorption bands that validate its structural and crystalline purity. Notably, carbonyl stretching vibration bands were detected at 1751.05 cm^{-1} and 1712.48 cm^{-1} (about ~ 1725), corresponding to the cyclohexyl carbonate and ester moieties, respectively. Aliphatic C–H stretching bands were detected at 2938.98 cm^{-1} and 2861.84 cm^{-1}, while aromatic C=C stretching was identified at 1612.2 cm^{-1}, indicating the existence of aromatic compounds. Additionally, a C–O–C/ether vibration was seen at 1033.66 cm^{-1}, confirming the existence of ether links in the structure. An intense band at 743 cm^{-1} was attributed to aromatic ring bending. The results align with previously reported data in the literature and validate CC's structural integrity as a BCS Class II ester prodrug (29).

The FTIR spectrum of PVP K30 exhibited a broad O–H stretching band at 3420–3430 cm^{-1}, a characteristic C=O lactam stretches at approximately 1656 cm^{-1}, and bands between 1400–1100 cm^{-1} corresponding to C–N and CH_2 bending modes, all indicative of its hydrophilic polymeric nature, corroborating findings by Bhatia and Devi (30).

The physical mixture (PM-PVP) of CC and PVP K30 demonstrated a clear overlap of the drug and polymer spectra, exhibiting no significant shifts, band broadening, or alterations in intensity. The ester C=O peak of CC remained distinct and unaltered, while the O–H band of PVP exhibited minimal change. The data indicate the absence of intermolecular contact or hydrogen bonding in the physical combination. This indicates that the drug and polymer merely coexist at the molecular level (24).

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The solid dispersion (SD) formulation exhibited significant spectral alterations. The ester carbonyl band of CC (~1725 cm^{-1}) decreased in intensity and merged with the amide C=O band of PVP, indicating the presence of hydrogen bonding. The broadening of the O–H region (3400–3200 cm^{-1}) and the shift in the fingerprint region indicate molecular interactions and amorphization. The shift in the spectrum indicates the molecular dispersion of CC within the PVP matrix. The lack of new bands suggests that the observed phenomena are due to non-covalent interactions, such as hydrogen bonding, aligning with previous studies (9).

The FTIR spectra of HPβCD exhibited a broad O–H stretching band (~3420–3430 cm^{-1}), C–H stretching at 2925 cm^{-1}, and C–O–C and glucose ring vibrations within the range of 1150–1020 cm^{-1}, characteristic of cyclodextrin derivatives (23).

There were no substantial changes in the position or shape of the peaks in the physical mixture (PM-HPβCD). The ester C=O and aromatic bands of CC stayed the same, and the functional group areas of HPβCD stayed the same. This proved that the drug and the carrier did not interact or include each other when they were not processed. The ICKN spectrum demonstrated significant reductions in the peak intensity of ester C=O and broadening of the O–H region, accompanied by the attenuation or absence of certain CC-specific peaks. The observed changes demonstrate non-covalent encapsulation of CC within the cyclodextrin cavity via hydrogen bonding and van der Waals interactions, without the formation of new chemical bonds (31). The disappearance of sharp CC peaks and their overlap with HPβCD bands confirm the formation of a real inclusion complex, consistent with observations in other documented host–guest complexes (9, 31). FTIR studies indicated that HPβCD and PVP K30 are compatible carriers for Candesartan Cilexetil. The physical mixtures of the drug with both carriers exhibited no spectral evidence of interaction. In contrast, the solid dispersion with PVP K30 demonstrated indications of hydrogen bonding and amorphization, while the inclusion complex with HPβCD showed band shifts consistent with molecular encapsulation. The findings demonstrate that both carriers effectively enhance the solubility of the drug at the molecular level, a phenomenon not observed in simple blending.

Powder X-Ray Diffraction (PXRD) Studies

The XRD analysis aimed to assess crystallinity changes across formulations and confirm solid-state transitions induced by complexation and dispersion processes. The XRPD pattern of pure

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CC showed multiple sharp peaks, with principal reflections at 2θ values of approximately 9.6°, 13.2°,16.5°, and 20.7°, indicating its very crystalline nature in accordance with the literature (9).

The ICKN spectra displayed a notable decrease in peak intensity, significant broadening, and a diffuse halo in the range of 10° to 30° 2θ, indicating partial amorphization. This indicates that the drug is confined within the HPβCD cavity and that the crystal lattice has been disrupted. Nonetheless, the remaining peaks indicate that complexation is incomplete or that crystalline CC persists. The results corroborate earlier studies on cyclodextrin-based inclusion systems, demonstrating that diminished peak intensity indicates drug entrapment and a reduction in crystallinity (16).

The SDRE formulation showed a broad, diffuse halo and no defined crystalline peaks, reflecting total amorphous transition. This may be attributed to PVP K30's ability to facilitate molecular dispersion and prevent recrystallization through hydrogen bonding. The findings corroborate previous studies indicating that PVP in CC formulations reduces crystallinity, thereby enhancing solubility and dissolution rates (32). It is widely recognized that a decline in three consecutive relative intensity percentage values in an XRD pattern indicates a reduction in the samples' crystallinity. Thus, these findings serve as verification of diminished crystallinity and, subsequently, phase change. The enhancement in bioavailability and solubility is due to an amorphous system, as reported (33).

Conclusion

This study's findings demonstrated that utilizing hydrophilic carriers in the formulation of solid dispersions via the solvent evaporation method and inclusion complexes through the kneading process significantly improved the solubility and dissolution rate of the poorly water-soluble drug Candesartan Cilexetil (CC). Furthermore, CC integrated into solid dispersion and inclusion complex formulations demonstrated significantly enhanced drug release rates relative to the pure drug sample, attributed to improved wettability, diminished crystallinity, and augmented drug–polymer interactions. These changes resulted in enhanced medication solubility and dissolving characteristics. Additionally, FTIR and XRD were employed to characterize all created CC formulations, confirming the absence of chemical interactions between the drug and excipients, as well as the transition of the drug into a less crystalline or amorphous state.

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Competing interest

The authors declare that they have no competing interests.

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