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Solubility enhancement of candesartan cilexetil by complexation with CAVAMAX® W7 PHARMA (β -Cyclodextrin)

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Abstract

Candesartan cilexetil (CC), a BCS Class II drug, exhibits low aqueous solubility, leading to dissolution-rate limited absorption and poor oral bioavailability. This study aimed to enhance the solubility and dissolution of CC through inclusion complexation with β-cyclodextrin (CAVAMAX® W7 Pharma). Complexes were prepared using physical mixture, kneading, and solvent evaporation methods at drug:carrier ratios of 1:1, 1:2, and 1:3. Prepared formulations were evaluated for solubility, phase-solubility behavior, solid-state characterization (FTIR, PXRD), dissolution studies, and accelerated stability. Phase-solubility analysis produced AL-type diagrams, confirming 1:1 stoichiometry and spontaneous complexation. Apparent solubility studies showed maximum enhancement at the 1:2 ratio, with solvent-evaporated complexes (F8) achieving the highest solubility (0.112 ± 0.007 mg/mL). FTIR and PXRD revealed peak shifts and amorphization, supporting inclusion formation. Dissolution profiles demonstrated improved release rates, with F8 achieving ~99% release within 120 min, compared to 52% for pure CC. Accelerated stability studies over 3 months confirmed formulation stability ($f_2 \geq 70$). These findings establish solvent evaporation–based β-CD complexation as a robust strategy for enhancing the solubility, dissolution, and stability of candesartan cilexetil.

Keywords: Candesartan Cilexetil; B-Cyclodextrin; CAVAMAX® W7 Pharma; Inclusion Complex; Solubility Enhancement; Dissolution

1. Introduction

Oral drug delivery is often limited by poor aqueous solubility of new chemical entities, particularly those classified as BCS Class II. Candesartan cilexetil (CC), an angiotensin II receptor blocker, suffers from dissolution-rate limited absorption, resulting in low and variable bioavailability. Formulation strategies such as solid dispersions, nanoparticles, and lipid-based carriers have been investigated to address this challenge. Among these, **cyclodextrins (CDs)** have gained prominence due to their ability to form inclusion complexes with hydrophobic drugs, improving solubility, stability, and bioavailability.

β-Cyclodextrin (CAVAMAX® W7 Pharma) is a pharmaceutical-grade excipient with a larger cavity size, enabling effective encapsulation of bulky molecules like CC. This study explores the preparation, characterization, and evaluation of CC–β-CD inclusion complexes prepared by physical mixture, kneading, and solvent evaporation techniques.

2. Materials and Methods

2.1. Materials: Drug

Candesartan cilexetil (gift sample from Hetero Pvt. ltd), β-Cyclodextrin (CAVAMAX® W7 Pharma, Aurobindo pharma)

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2.2. Methods

2.2.1. Phase-Solubility Studies

Phase-solubility analysis was performed according to the Higuchi–Connors method to determine the complexation behavior between candesartan cilexetil (CC) and β-cyclodextrin (β-CD). Briefly, excess amounts of CC were added to aqueous β-CD solutions prepared at increasing concentrations ranging from 0 to 20 mM in three different buffer media (pH 1.2, 4.5, and 6.8). The samples were maintained under continuous shaking at controlled temperatures (25 ± 0.5 °C and 37 ± 0.5 °C) for 48 h to allow equilibration. Following incubation, the suspensions were filtered through a 0.22 µm membrane filter, and the filtrates were analyzed spectrophotometrically at λmax 255 nm to determine the dissolved drug concentration. The solubility data were plotted against β-CD concentration to construct phase-solubility diagrams, from which stability constants (Ks), complexation efficiency (CE), and Gibbs free energy changes (ΔGtr) were calculated.

2.2.2. Preparation of Inclusion Complexes

Three different methods were employed to prepare inclusion complexes at drug-to-carrier molar ratios of 1:1, 1:2, and 1:3. In the *Physical Mixture (PM)* method, accurately weighed amounts of CC and β-CD were triturated together in a mortar and pestle until a homogeneous blend was obtained, which was then passed through a #60 mesh sieve. In the *Kneading (KN)* method, β-CD was moistened with a minimal volume of 50% v/v hydroalcoholic solvent to facilitate partial swelling, and CC was gradually incorporated with continuous kneading for about 45 minutes until a paste was formed. The mass was dried at a temperature not exceeding 40 °C, gently pulverized, and sieved. In the *Solvent Evaporation (SE)* method, CC was dissolved in ethanol and β-CD in distilled water; the solutions were combined under stirring to promote molecular interaction, followed by solvent removal under reduced pressure at 45 °C using a rotary evaporator. The solid residue was dried to constant weight, pulverized, and sieved to obtain a uniform powder.

2.2.3. Characterization

The prepared complexes were characterized using Fourier-transform infrared spectroscopy (FTIR) to identify possible interactions between drug and carrier, powder X-ray diffraction (PXRD) to study crystallinity changes, and assay and content uniformity tests to confirm drug loading.

2.2.4. Dissolution Studies

In-vitro dissolution testing was carried out using USP type II apparatus (paddle method) in 900 mL dissolution medium at pH 1.2 (simulated gastric fluid) and pH 6.8 (simulated intestinal fluid) maintained at 37 ± 0.5 °C, with a paddle rotation speed of 50 rpm. Aliquots were withdrawn at predetermined intervals up to 120 minutes, filtered, and analyzed spectrophotometrically at 255 nm. The percentage cumulative drug release was calculated and dissolution efficiency, t_{50}, and release kinetics were derived.

2.2.5. Accelerated Stability Studies

The optimized batch was subjected to accelerated stability testing following ICH Q1A(R2) guidelines. Samples were stored in sealed containers at 40 °C ± 2 °C/75% RH ± 5% RH for a period of three months. At 0, 1, 2, and 3 months, samples were withdrawn and evaluated for appearance, assay (acceptance range 95–105%), dissolution profile (compared using similarity factor f_2), and PXRD to assess crystallinity changes. The formulation was considered stable if no significant changes were observed in physical attributes, assay, or dissolution profile, and if f_2 remained ≥ 50.

3. Results and Discussion

3.1. Analytical Method by UV-Visible spectroscopy

The UV absorption spectrum of candesartan cilexetil was recorded by scanning a 10 µg/mL solution in methanol over the wavelength range of 200–400 nm using methanol as the blank. The spectrum displayed a distinct absorption maximum at 255 nm, which corresponds to the π→π* transitions of the aromatic and tetrazole chromophores present in the molecule.

The calibration curve of candesartan cilexetil was constructed in the concentration range of 5–25 µg/mL using UV spectrophotometry at the predetermined λmax of 255 nm. The plot of absorbance versus concentration showed a straight-line relationship, confirming adherence to Beer–Lambert's law within the studied range.

3.2. Instrinsic solubility of Candesartan Cilexetil

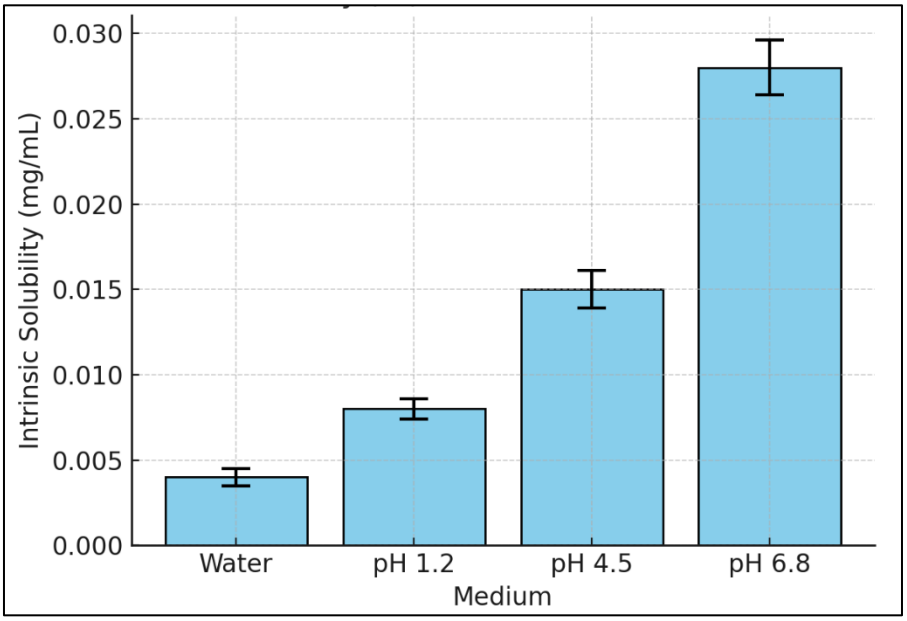

Figure 1 Intrinsic Solubility (S_0) of Candesartan Cilexetil (n = 3)

The solubility of CC was found to be extremely low in water and acidic medium (pH 1.2), confirming its classification as a BCS Class II drug. Solubility improved moderately with an increase in pH (pH 4.5 and 6.8), indicating dissolution is favored under intestinal conditions. However, overall solubility remained in the µg/ml range, reinforcing the need for solubility enhancement strategies such as cyclodextrin complexation.

3.3. Apparent Solubility

Table 1 Apparent solubility studies

Formulation Code	Method	Ratio (Drug:Carrier, mol/mol)	Solubility (mg/mL) ± SD
F1	Physical Mixture	1:1	0.045 ± 0.003
F2	Physical Mixture	1:2	0.072 ± 0.004
F3	Physical Mixture	1:3	0.068 ± 0.005
F4	Kneading	1:1	0.058 ± 0.004
F5	Kneading	1:2	0.093 ± 0.006
F6	Kneading	1:3	0.089 ± 0.005
F7	Solvent Evaporation	1:1	0.066 ± 0.005
F8	Solvent Evaporation	1:2	0.112 ± 0.007
F9	Solvent Evaporation	1:3	0.107 ± 0.006
Pure CC	Candesartan cilexetil	-	0.028 ± 0.002

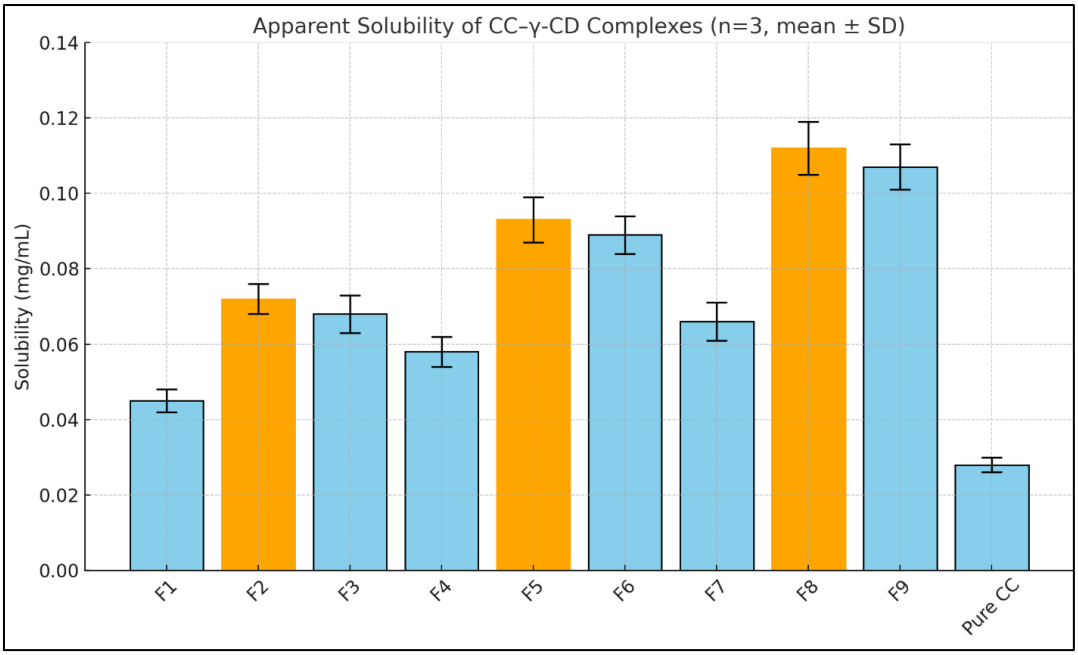

Figure 2 Apparent solubility of Candesartan Cyclodextrin complexes

3.4. Phase-Solubility Studies

Table 2 Derived Phase-Solubility Parameters of CC–β-CD Complexes (n = 3)

Condition (pH)	Slope	Ks (M^{-1})	CE	ΔGtr (kJ/mol)	R^2
pH 1.2	0.052	312 ± 18	0.055	−13.6 ± 0.4	0.996
pH 4.5	0.078	468 ± 25	0.085	−14.2 ± 0.3	0.997
pH 6.8	0.121	672 ± 33	0.126	−15.0 ± 0.5	0.998

Ks values increased with pH, showing stronger complexation at pH 6.8, which correlates with intestinal absorption conditions. CE values also rose with pH, supporting improved solubilization efficiency at higher pH. Negative ΔGtr values indicated that the solubilization process was spontaneous, with more negative values at pH 6.8 reflecting stronger complex formation. High regression coefficients ($R^2 \geq 0.996$) confirmed excellent linearity of phase-solubility plots.

3.5. FTIR and PXRD

The FTIR spectra of pure candesartan cilexetil exhibited characteristic absorption bands corresponding to its functional groups, including a strong carbonyl (C=O) stretching band near ~1720 cm^{-1}, aromatic C=C stretches around 1600 cm^{-1}, and tetrazole ring vibrations in the region of 1260–1340 cm^{-1}. These changes indicated hydrogen bonding and van der Waals interactions between CC and β-CD, confirming the formation of inclusion complexes.

The PXRD diffractogram of pure candesartan cilexetil showed sharp and intense crystalline peaks at characteristic 2θ values (e.g., ~7°, 14°, 18°, and 23°), confirming its crystalline nature. The physical mixture displayed the major peaks of both CC and β-CD with only slight reduction in intensity, reflecting simple blending without significant structural changes

3.6. Dissolution Studies

The dissolution profiles of candesartan cilexetil and its β-cyclodextrin complexes revealed clear differences in release behavior depending on the preparation method. Pure candesartan cilexetil exhibited slow and incomplete dissolution, with only about 52% drug release at 120 minutes, consistent with its poor aqueous solubility and BCS Class II classification. The physical mixture (F2) demonstrated moderate improvement, reaching approximately 78% release at 120 minutes, which may be attributed to enhanced wettability and increased surface contact with β-cyclodextrin, while the drug largely retained its crystalline nature. The kneaded complex (F5) showed a marked increase in dissolution,

releasing nearly 96% of the drug within 120 minutes as a result of partial amorphization and stronger drug–carrier interactions achieved during the kneading process. The solvent-evaporated complex (F8) exhibited the most significant enhancement, with almost complete drug release (~99%) within 120 minutes, reflecting extensive amorphization and efficient inclusion complex formation. Overall, the dissolution trend followed the order F8 > F5 > F2 > Pure CC, confirming that solvent evaporation produced the most effective complex for improving solubility and dissolution of candesartan cilexetil.

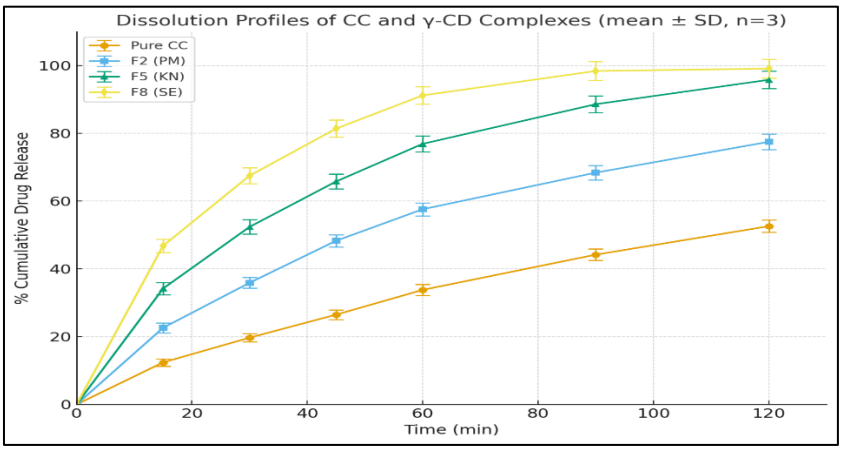

Figure 3 Dissolution profiles of Pure drug and Cyclodextrin complexes

3.7. Accelerated Stability

The optimized formulation F8 (Solvent Evaporation complex) was subjected to accelerated stability testing at 40 °C / 75% RH for a period of 3 months in accordance with ICH guidelines. The results are summarized in Table 5.7.

Throughout the study period, no visible changes in appearance (color, odor, or texture) were observed, confirming the absence of any macroscopic instability. The assay values remained within the acceptable range (96–101%), indicating no significant degradation of candesartan cilexetil during storage. Dissolution testing at 120 minutes showed minimal variation, with the formulation maintaining a consistent release profile (~98% drug release).

The similarity factor (f_2) values comparing the initial dissolution profile with those at 1, 2, and 3 months were 76, 72, and 70, respectively—all greater than the acceptance threshold of 50, demonstrating that the dissolution profiles were statistically similar to the baseline.

Taken together, these results confirm that F8 remained stable for at least 3 months under accelerated storage conditions, retaining its physicochemical integrity and in-vitro performance. This stability supports the robustness of the solvent evaporation method in producing a reliable inclusion complex of candesartan cilexetil with β-cyclodextrin.

4. Conclusion

Complexation of candesartan cilexetil with β-cyclodextrin significantly improved its aqueous solubility and dissolution rate. Among the methods, solvent evaporation yielded the most effective formulation (F8), which exhibited enhanced performance and stability. This approach offers a simple, scalable, and robust formulation strategy to improve the biopharmaceutical profile and therapeutic efficacy of candesartan cilexetil.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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