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Research Article

DEVELOPMENT AND EVALUATION OF CONTROLLED POROSITY OSMOTIC TABLETS OF CANDESARTAN CILEXETIL USING INCLUSION COMPLEX SYSTEM

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ABSTRACT

Objective: This study aims to enhance the solubility of BCS Class-II drug candesartan cilexetil (CC) by forming inclusion complexation with hydroxypropyl β-cyclodextrin (CDs) and develop a controlled-release osmotic tablet for 24-h release.

Methods: Solubility of Candesartan was enhanced using hydroxypropyl β-CDs at a molar ratio1:1 and analyzed for drug content and drug release profile. Fourier transform infrared interaction studies were conducted in drug complex and excipients. Core tablets were prepared with various ratios of osmogens (mannitol: Lactose monohydrate). Pre-compression studies were performed, and cellulose acetate solution containing sorbitol as pore-forming agent was used to coat the tablet cores, achieving 3% and 5% weight gain. The core tablets were subjected to post-compression tests assessing parameters such as thickness, weight variation, hardness, friability, and drug content, while the coated tablets underwent *in vitro* dissolution studies. Data obtained were subjected to drug release kinetics and formulation F6 was subjected to stability studies.

Results: Characterization confirmed good flow properties, mechanical stability, and uniform drug content. Formulation F6 coated with cellulose acetate, showed 97.33% drug release at 24 h, following zero-order kinetics. Stability studies indicated that F6 remained stable for 3 months, with no notable changes in attributes such as appearance, drug content, and dissolution profile.

Conclusion: This study successfully formulated a controlled drug delivery system for CC using controlled porosity osmotic delivery suggesting its potential for further development and clinical evaluation to enhance patient compliance and therapeutic efficacy.

Keywords: Candesartan cilexetil, Controlled porosity osmotic pump, Osmogen, Mannitol, Lactose monohydrate, Cellulose acetate.

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INTRODUCTION

The controlled-porosity osmotic tablet is created by coating a core tablet with a semipermeable membrane that incorporates channeling pore formers. In contrast to traditional osmotic pumps, which feature an opening, the drug release from porosity osmotic tablets occurs through the pores that form within the semipermeable wall after ingestion. The hydrostatic pressure generated in the tablet once it absorbs fluid, combined with the dissolution of the pore-forming agents in the membrane, allows the drug to be released from the core during the dissolution phase. This hydrostatic pressure can be produced by an osmotic agent, the drug itself, or both, once water penetrates the semipermeable membrane. After pore formation, both water and solutes can pass through the membrane [1,2].

Candesartan Cilexetil (CC) is a new angiotensin II antagonist with low bioavailability (under 40%). It is a BCS Class-II drug and a prodrug that undergoes complete bioactivation through ester hydrolysis in the gastrointestinal tract, converting to candesartan [3,4]. This medication is utilized for managing heart failure and hypertension. The half-life of CC and its low bioavailability necessitates frequent administration to maintain effective levels. Extended-release formulations are among the most efficacious systems, designed to reduce the frequency of administration while improving patient adherence compared to conventional tablets [5,6].

Cyclodextrins (CDs) are non-reducing cyclic oligosaccharides made up of α-D-glucopyranose units connected by (α-1, 4) bonds. They have a hydrophilic outer surface and a hydrophobic central cavity, with the outer part being soluble in water, while the hydrophobic interior provides a suitable environment for non-polar molecules of the right size [7]. CDs are commonly employed in oral pharmaceutical formulations as inclusion complexes, enhancing solubility, dissolution rates, stability, and bioavailability [8,9].

The drug release is modulated by incorporating an inclusion complex in the osmotic tablets. Such osmotic tablets manage drug delivery in a controlled manner, which consequently improves bioavailability and lessens the frequency of drug administration. This study seeks to evaluate how the hydroxy propyl β-CDs (HPβCD) complex influences the drug release properties of controlled porosity osmotic tablets containing CC.

MATERIALS AND METHODS

Materials

CC was gifted by Sai Mirra Innopharm, Chennai. HPβCD was brought from Merck, lactose monohydrate, mannitol, sodium CMC, magnesium stearate, cellulose acetate, polyethylene glycol 400, and other reagents were of analytical grade.

Methods

Kneading method

CC-HPβCD inclusion complex was developed using kneading technique in 1:1 ratio. CC and HPβCD were triturated in a mortar with a sufficient amount of methanol. The drug was gradually incorporated into the mixture. The resulting thick slurry was kneaded for 15 min and dried at 55°C until dry. The mixture was then passed through mesh No. 120 [10,11].

Evaluation of HPβCD inclusion complex

The HPβCD inclusion complex was assessed and characterized using the following methods.

Saturation solubility

The solubility levels of CC and complexed CC with HPβCD were measured in various solvents, including water, pH 6.5 phosphate buffer, and 0.1N hydrochloric acid. Excess of drug was added to the solvents until saturation was reached by shaking with continuous agitation. Then the mixtures were filtered and absorbance measured at 254 nm using an ultraviolet (UV) spectrophotometer (UV-1700, Shimadzu) [12].

Studies on drug-excipients compatibility

It is crucial to determine the compatibility between the drug and excipients under experimental conditions. This compatibility was evaluated using Fourier transform infrared (FTIR) spectroscopy. FTIR spectra for the drug and its physical mixture with the inclusion complex were obtained using a FTIR spectrophotometer (FTIR-A213748, Shimadzu, Japan) within the range of 4000–400 cm^{-1} to identify potential interactions. Scanning was conducted at a speed of 2 mm/sec and a resolution of 4 cm^{-1}. The resulting scans were analyzed for significant drug peaks, any shifts or masking of these peaks, and the emergence of new peaks that indicate interactions with the polymer [13].

Percentage practical yield

The process's effectiveness is assessed by the yield obtained. The percentage practical yield was calculated to determine the method's efficiency. The HPβCD complex was weighed to evaluate the practical yield with the formula:

% practical yield = Practical mass of inclusion complex/Theoretical mass (drug + carrier) × 100.

***In vitro* drug release profile for complex drug powder and pure drug**

In vitro, release tests for both the CC-HPβCD complex and the pure drug CC were conducted using a USP Type II dissolution apparatus with a paddle method at 75 rpm and a temperature of 37±0.5°C. The dissolution medium comprised 900 mL of pH 6.5 phosphate buffer with 0.35% polysorbate 20. Each test involved a drug complex equivalent to 16 mg of CC. At predetermined time intervals, 5 mL samples of the dissolution medium were taken, diluted, and analyzed for absorbance at 254 nm using a UV-Vis spectrophotometer (UV–1700, Shimadzu). The volume removed at each interval was replaced with a fresh dissolution medium to ensure sink conditions. The released amount of CC was calculated and plotted over time, compared to the pure drug [14].

Drug content

A precise amount of the complex was weighed and dissolved in pH 6.5 phosphate buffer with 0.35% polysorbate 20. This solution was suitably diluted with the same buffer and analyzed for drug content using a UV-Vis spectrophotometer (UV–1700, Shimadzu) at 254 nm.

Preparation of core tablet

The formulations for all batches are outlined in Table 1. The drug complex was first sieved through a 20# screen, while lactose monohydrate, sodium CMC, and mannitol were passed through a 40# screen to eliminate any clumps. The sifted powders were then thoroughly mixed using a rapid mixer granulator. This dry mixture was kneaded for 2 min and 30 s. The resultant dry mass was moved to a tray dryer and allowed to dry for 15 min using the following parameters: Airflow −40, temperature −40°C, duration −15 min. Once dried, the granules were sifted through a 20# screen, and these granules were lubricated with magnesium stearate for 3 min in a blender operating at 10 rpm. The core tablet was then compressed directly using the prepared blend with 6 mm punches on a rotary tableting machine (Rimek RSB-4 Minipress, Cadmach) [15].

Table 1: Composition of core tablets

Ingredients	Formulation					
	F1	F2	F3	F4	F5	F6
Candesartan inclusion complex (mg) equivalent to 16 mg	64	64	64	64	64	64
Lactose monohydrate	57	49.5	42	34.5	27	19.5
Mannitol	7.5	15	22.5	30	37.5	45
Maize starch (mg)	15	15	15	15	15	15
Sodium carboxy methyl cellulose (mg)	4.75	4.75	4.75	4.75	4.75	4.75
Magnesium stearate (mg)	1.75	1.75	1.75	1.75	1.75	1.75

Coating process

The coating composition is given in Table 2. A precisely weighed quantity of cellulose acetate was added to the coating solvent (Acetone: Isopropyl alcohol; 9:1) and stirred using a mechanical stirrer. Sorbitol was added as a pore former and the polyethylene glycol 400 was added as a plasticizer. The coating process was performed using Sams India Coater Machine by setting the parameters of initial temperature of 30°C, bed temperature of 28°C rotation speed of 8–15 rpm, and atomization at psi of 2.0. The tablets were coated to achieve an increase in weight of 3% (F1-F6) and 5% (F7-F12) [16].

Evaluation of pre-compression parameters of drug with excipient

Before the granules were compressed into tablets, they were assessed for various properties, such as the angle of repose (Θ°), bulk density, tapped density, compressibility index, and Hausner's ratio (HR) [17-19].

Evaluation of core and coated osmotic tablet

The prepared core tablets were evaluated for weight variation, drug content, friability, hardness, thickness. The coated tablet was evaluated by the *in vitro* dissolution studies, drug release kinetics, and stability studies [20].

Weight variation

For the weight variation test, 20 tablets from each batch were individually weighed using a Sartorius electronic balance and compared to the average value. This test was conducted in accordance with official standards.

Thickness. Friability and hardness

Tablet thickness which is an important characteristic is carried out using Vernier calipers. Ten tablets were weighed to record the initial weight. The tablets were then placed in the Roche friabilator and tested for 4 min at 25 rpm. This is followed by reweighing after the tablets are dusted. The percent weight loss was calculated using

$$\text{Percentage loss} = \frac{\text{Initial weight of tables} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

The hardness in kg/cm^2 of the tablets was determined using a Monsanto hardness tester. A tablet was placed between the anvils, and the force required to break the tablet was recorded. The average of three readings was taken and noted [21].

Drug content

The assay of the tablets was assessed. A random selection of 20 tablets was weighed and ground into a powder. To a precise amount which contains 45 mg of CC, 5 mL of acetonitrile was added and dissolved by sonication for 5 min. The volume was then adjusted to 100 mL using pH 6.5 phosphate buffer with 0.35% polysorbate 20, and the resulting solution was filtered through a Whatman filter. The absorbance was recorded at 254 nm using a UV-Vis spectrophotometer (UV–1700, Shimadzu) [22].

Table 2: Components of coating solution

Ingredients	Quantity
Cellulose acetate (g)	4
Sorbitol (g)	0.88
Polyethylene glycol 400 (g)	0.50
Iron oxide red (g)	0.05
Acetone (mL)	96.84
Isopropyl alcohol (mL)	10.76

Evaluation of coated controlled porosity Osmotic tablet

In vitro dissolution studies

The release of CC from the prepared osmotic tablets was examined using USP II paddle dissolution apparatus (TD-08L-USA). 900 mL of pH 6.5 phosphate buffer with 0.35% polysorbate 20 served as the dissolution medium. Polysorbate 20 was used to maintain sink conditions during dissolution [23,24]. The paddle was set to rotate at 50 rpm and the temperature was consistently maintained at 37°C. At predetermined time intervals (2, 4, 8, 16, 20, and 24 h), 10 mL of samples were pipetted out and replaced with equal volume of dissolution medium. The samples were filtered and diluted with the medium and determined spectrophotometrically at 254 nm.

Stability studies

Stability testing is carried out to study the changes which occur over time under environmental factors like temperature, humidity, and light, helping to determine shelf-life and recommend storage conditions. The ICH-Q1A (R2) guidelines determine the test conditions based on climatic analysis from various countries. Stability studies should leverage knowledge from the drug substance's properties, stability studies, and clinical formulation experience. Expected storage changes and the rationale for selected test attributes should also be specified [25]. The optimized tablets were placed in HDPE containers and placed in Humidity Chamber at 40°C/75% RH. At 3 months of storage, the tablets were evaluated for *in vitro* drug release and assay.

Statistical analysis

A one-way analysis of variance was used to assess the significance of differences observed in the outcomes of the formulations being studied. The significance level was set at α=0.05; any value below this threshold was considered statistically significant, while values above it were regarded as statistically insignificant.

RESULTS AND DISCUSSION

Based on the results obtained from the study by Aziz and Al-Khedairy [11], the best complex for increased dissolution was obtained using 1:1 CC: HPCD molar ratio, and hence, no other complex was prepared

Saturation solubility

The solubility study was conducted at different pH and with 0.35% polysorbate 20 to determine the saturation solubility of CC. As illustrated in Table 3, the formation of the complex with HPβCD and the addition of polysorbate 20 enhanced CC's solubility significantly ($p<0.05$). These findings demonstrate that HPβCD serves as an effective carrier for improving the solubility of poorly soluble medications. CC showed 8.4–20.8 fold increase in solubility. Addition of anionic surfactant like polysorbate 20 to the complex system enhanced the solubilization. This is attributed to CC and the amphiphile molecules forming inclusion complex in aqueous solution [20].

FTIR spectrum

The infrared spectroscopy (IR) spectra for the pure drug, the candesartan/HPβCD complex (1:1), and physical mixtures with excipients are depicted in Figs. 1-3, respectively. The spectra obtained showed that the absorption peaks of CC and its physical mixtures retained consistent band profiles, implying no interaction between them and confirming good compatibility between CC and HPβCD. The

Table 3: Solubility studies

Sl. No.	Solvent	Solubility (mg/mL) (mean±SD)	Solubility enhancement ratio
1.	Distilled water	0.007±0.0005	-
2.	0.1N Hcl medium (pH 1.2)	0.009±0.002	-
3.	Buffer medium (pH 6.5)	0.02±0.03	-
4.	0.1N Hcl medium (pH 1.2) for CC: HPβCD complex	0.076±0.02	8.4
5.	Buffer medium (pH 6.5) for CC: HPβCD complex	0.32±0.05	16.0
6.	0.1N HCL+0.35% polysorbate 20 for CC: HPβCD complex	0.093±0.007	10.3
7.	pH 6.5 phosphate buffer+0.35% polysorbate 20 for CC: HPβCD complex	0.416±0.013	20.8

IR spectrum of the inclusion complex showed distinct peaks at the wave numbers associated with both pure CC and hydroxypropyl β-CDs, along with the excipients. This confirms the formation of an inclusion complex and indicates that there were no interactions between the drug, HPβCD, and the excipients.

Drug content and percentage yield

The percentage yield of the inclusion complex was 94.7% the high value shows the efficiency of kneading technique for the preparation of the inclusion complex. The percentage drug content at 98.4% indicates uniform dispersion of the drug and kneading as a highly efficient method for the preparation of inclusion complex.

***In vitro* drug release profile for complex drug powder and pure drug**

The results of percentage drug release for CC: HPβCD complex and pure drug are shown in Fig. 4 with improved dissolution for the complex.

Characterization of osmotic tablets

The core tablet is formulated by mixing the complex drug with required excipients then the granulated mixture is compressed directly using 6 mm punch in rotary press and the core tablet is evaluated. Then the core tablet is coated with the coating solution which acts as a semi-permeable membrane and which was evaluated.

Evaluation of pre-compression granules

As displayed in Table 4, the angle of repose for formulations F1-F6 ranged from 19.8 to 26.31, indicating satisfactory flow characteristics. The Carr index values for all formulations were found to be under 20, demonstrating acceptable flow properties. The HR values were recorded between 1.14 and 1.21. Pre-compression assessments revealed that all granules exhibited adequate flowability and compressibility.

Evaluation of compressed granules (core tablets)

Evaluation tests for tablets such as weight variation, hardness, friability, and drug content and thickness of each batch are represented in Table 5. Weight variation for all batches was found to be within range. All batches were found to have friability of <1%, which ensures that tablets can withstand forces during manufacturing, transportation, or storage until they are used. The hardness of the tablets was between 4.7 and 5.2 kg/cm^2 drug content of all batches was found within limit (90–110%).

Evaluation of coated tablets

In vitro dissolution studies

Core of formulations F1 to F12 contained inclusion complex which was further coated with a weight gain of 3% (F1-F6) and 5% weight gain (F7-F12). The *in vitro* dissolution profile is shown in Figs. 5 and 6. F1, F2, and F3 had drug release of 70.94–81.92% at the end of 24 h. Moreover,

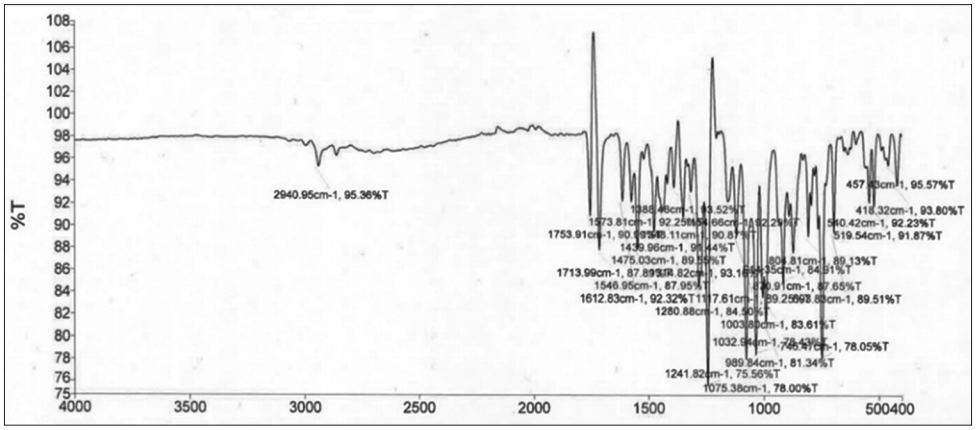

Fig. 1: Fourier transform infrared of candesartan cilexetil

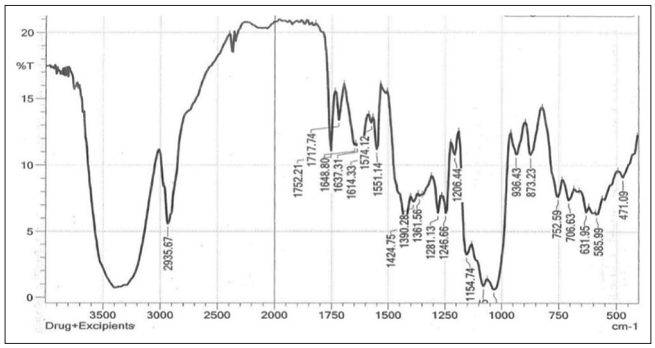

Fig. 2: Fourier transform infrared of candesartan cilexetil: HPβCD complex

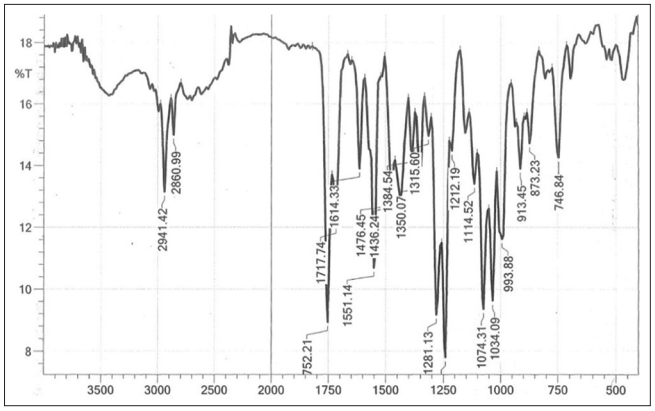

Fig. 3: Fourier transform infrared of candesartan cilexetil and excipients

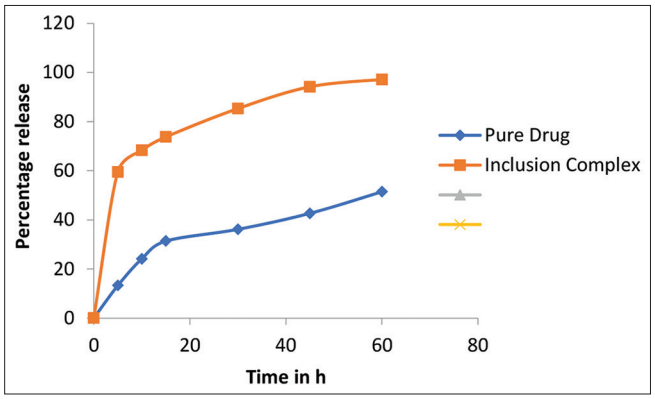

Fig. 4: *In vitro* release comparison of pure drug with inclusion complex

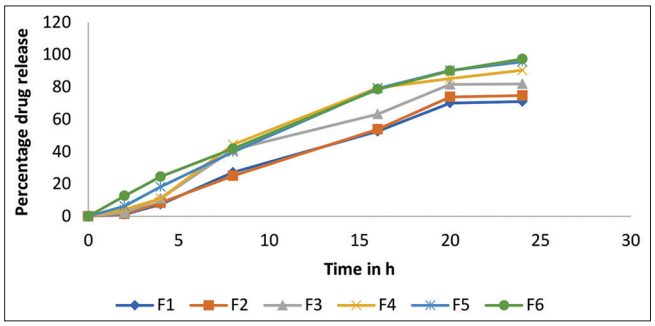

Fig. 5: Cumulative *in vitro* drug release study of CPOP Candesartan Cilexetil (F1-F6)

at 2 h, there was a release of 1.17–2.18% which is not adequate. On increase in mannitol, it was seen from F4-F5 the drug release at 24 h was 90.33–95.57% and the release at 2 h was 4.25–6.32%. The optimum drug release was seen in F6 which released 95.33% of the drug at 24 h and 12.56 at 2 h which is good release pattern. This can be accounted for the increase in mannitol which is used as osmogen. Mannitol plays a more significant role than lactose by providing the driving force to increase the rate of drug release. The pore-forming agent added was kept constant. Increase in coating to 5% caused a significant decrease in drug release which is seen in F7 to F12. F7 showed a drug release at 24 h of 59.63% while it was 72.38% for F12.

Drug release kinetic study

To analyze the release rate from the CC-controlled porosity osmotic tablet (F6), several kinetic models, including zero order, first order, Higuchi, and Korsmeyer-Peppas, were applied as detailed in Table 6. The release data were analyzed using various kinetic models to establish drug release kinetics and mechanisms. The slope of the relevant plots was utilized to compute the release constant, with the regression coefficient (R^2) calculated. The *in vitro* drug release profile for the CC-controlled porosity osmotic tablet best conformed to zero-order kinetics, as evidenced by the highest linearity of the plots, with a correlation coefficient (R^2) of 0.9725.

Stability studies

Accelerated stability testing of the controlled porosity osmotic tablet was conducted in accordance with ICH guidelines to evaluate whether storage conditions affect the tablets. The optimized formulation F6 was placed at 40°C±2°C with 75±5% RH for 3 months. The physical characteristics, drug content, and dissolution profile were assessed after this period, as presented in Table 7. The results indicated no

Table 4: Evaluation of pre-compression granules of F1-F6

Formulation code	Bulk density (mean±SD)	Tapped density (mean±SD)	Hausner's ratio	Carr's index	Angle of repose (mean±SD)
F1	0.547±0.34	0.654±0.74	1.19	16.36	26°31'±0.21
F2	0.599±0.45	0.701±0.52	1.17	14.55	22°58'±0.15
F3	0.586±0.52	0.672±0.17	1.14	12.79	24°11'±0.23
F4	0.526±0.12	0.625±0.35	1.18	15.84	19°80'±0.36
F5	0.531±0.37	0.643±0.51	1.21	17.41	21°26'±0.18
F6	0.559±0.26	0.663±0.44	1.18	15.68	22°14'±0.11

Table 5: Evaluation of core tablets of F1-F6

Formulation code	Weight variation (mean±SD)	Thickness (mm) (mean±SD)	Friability (%) (mean±SD)	Hardness kg/cm^2 (mean±SD)	Drug content (%) (mean±SD)
F1	149±2.32	4.79±1.6	0.66±0.02	4.7±0.12	99.4±1.61
F2	149±1.98	4.75±1.7	0.67±0.02	5.0±0.05	99.8±1.00
F3	150±2.1	4.72±15	0.66±0.01	4.9±0.18	100.14±0.68
F4	151±1.67	4.73±0.5	0.66±0.01	5.2±0.22	100.92±0.89
F5	152±2.21	4.74±1.3	0.67±0.02	5.1±0.19	101.12±0.68
F6	151±2.45	4.70±1.6	0.66±0.01	5.1±0.21	100.3±1.61

Table 6: Kinetic model

Formulation code	Kinetic models				
	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas n	R^2
F6	0.9725	0.8425	0.9239	0.421	0.9232

Table 7: Stability studies of optimized formulation F6

Test	Initial	40°C/75% RH
Physical appearance	Pale red colored smooth-faced tablet	No change
Friability %	0.66±0.01	0.62±0.23
Assay %	100.3±1.61	100.54±0.75
Dissolution release profile		
2 h	12.56±0.16	12.08±0.10
8 h	41.77±1.26	44.96±0.94
24 h	97.33±0.15	95.78±2.25

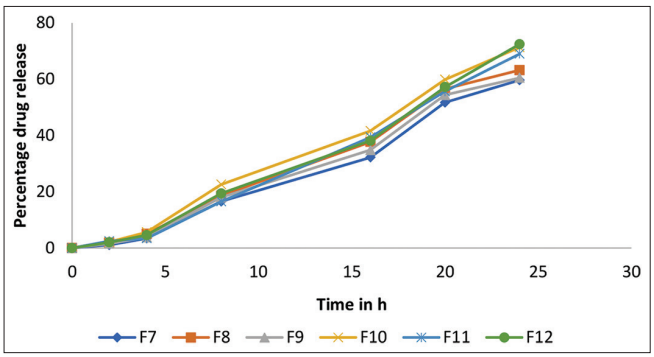

Fig. 6: Cumulative *in vitro* drug release study of CPOP Candesartan Cilexetil (F7-F12)

significant differences between the initial and aged-controlled porosity osmotic tablets. The color, friability, drug content percentage, and drug release remained unchanged. The optimized formulation was deemed physically and chemically stable under accelerated stability conditions.

CONCLUSION

The controlled drug delivery system of CC was developed using the inclusion complex kneading method for a controlled porosity osmotic tablet. This approach aimed to raise the drug's bioavailability and improve patient compliance by reducing the administration frequency to once daily. *In vitro* studies have demonstrated the system's potential for delivering CC with good stability and release profiles. Specifically, Formulation F6 exhibited a controlled release of CC, achieved through the use of hydroxypropyl β-CDs to alter the dissolution profile and control its release through the osmotic delivery system. This innovative drug delivery system presents a promising solution for improving CC solubility and offering controlled release and potentially enhancing patient adherence.

CONFLICTS OF INTEREST

It is hereby stated that this paper has no conflict of interest.

REFERENCES

1. Babu A, Rao MP, Vijaya Rathna J. Controlled porosity osmotic pump tablets-an overview. J Pharm Res Health Care. 2010;2(1):114-26.
2. Choudhary S, Subrahmanyam CV, Priyanka K. Osmotic drug delivery system of nicorandil: Design and evaluation. Int J Appl Pharm. 2024;16(3):119-28. doi: 10.22159/Ijap.2024v16i3.50298
3. Oparil S. Newly emerging pharmacologic differences in angiotensin II receptor blockers. Am J Hypertens. 2000;13(1 Pt 2):18S-24. doi: 10.1016/s0895-7061(99)00250-2, PMID: 10678284
4. Hübner R, Högemann AM, Sunzel M, Riddell JG. Pharmacokinetics of candesartan after single and repeated doses of candesartan cilexetil in young and elderly healthy volunteers. J Hum Hypertens. 1997 Sep 11;2(Suppl 2):S19-25. PMID: 9331000
5. Amer AM, Allam AN, Abdallah OY. Preparation, characterization and *ex vivo-in vivo* assessment of candesartan cilexetil nanocrystals via solid dispersion technique using an alkaline esterase activator carrier. Drug Dev Ind Pharm. 2019;45(7):1140-8. doi: 10.1080/03639045.2019.1600533, PMID: 30912678
6. Alatas F, Ratih H, Sutarna TH, Fauzi ML. The binary and ternary amorphous systems of candesartan cilexetil preparation to improve its solubility. Int J Appl Pharm. 2024;16(5):368-73. doi: 10.22159/ijap.2024v16i5.51141
7. Jansook P, Kulsirachote P, Asasutjarit R, Loftsson T. Development of celecoxib eye drop solution and microsuspension: A comparative investigation of binary and ternary cyclodextrin complexes. Carbohydr Polym. 2019;225:115209. doi: 10.1016/j.carbpol.2019.115209, PMID: 31521306
8. Salústio PJ, Pontes P, Conduto C, Sanches I, Carvalho C, Arrais J, *et al*. Advanced technologies for oral controlled release: Cyclodextrins for oral controlled release. AAPS PharmSciTech. 2011;12(4):1276-92. doi: 10.1208/s12249-011-9690-2, PMID: 21948320
9. Todkar S, Dhole S, Umate T, Kulkarni N. Cyclodextrin in novel formulations and solubility enhancement techniques: A review. Int J Curr Pharm Res. 2024;16(2):9-18. doi: 10.22159/ijcpr.2024v16i2.4032
10. Cheirsilp B, Rakmai J. Inclusion complex formation of cyclodextrin

with its guest and their applications. Biol Eng Med. 2016;2(1):1-6. doi: 10.15761/BEM.1000108
11. Aziz GM, Al-Khedairy EB. Solubility and dissolution enhancement of candesartan cilexetil by complexation with cyclodextrin. Int J Drug Deliv Technol. 2024;14(1):257-64. doi: 10.25258/ijddt.14.1.37
12. Rani AP, Murthy VS, Madhavi BR. Comparative study on the preparation and characterization of inclusion complexes of BCS class II drug with cyclodextrins. Adv Res Pharm Biol. 2013;3(II):420-5.
13. Sravya M, Deveswaran R, Bharath S, Basavaraj BV, Madhavan V. Development of orodispersible tablets of candesartan cilexetil-β-cyclodextrin complex. J Pharm (Cairo). 2013;2013:583536. doi: 10.1155/2013/583536, PMID: 26555987
14. Shah M, Mehta T, Amin A. Preparation and characterization of inclusion complex of a calcium channel blocker. Int J Pharm Biomed Sci. 2011;2:1731-8.
15. Shirse P, Rao KS, Iqbal MM. Formulation and evaluation of cyclodextrin inclusion complex tablets of water insoluble drug-glimipiride. Int J Res Pharm Chem. 2012;2(1):222-8.
16. Kaushik S, Pathak K. Development and evaluation of monolithic osmotic tablet of ketoprofen: Using solid dispersion technique. Int J Pharm Pharm Sci. 2016;8(12):41-7. doi: 10.22159/ijpps.2016v8i12.11437.
17. Aulton ME, Taylor KM. Aulton's Pharmaceutics: The Design and Manufacturing of Medicines. 3rd ed. London: Elsevier; 2013. p. 329, 335-53.
18. Ammar HO, Makram TS, Mosallam S. Effect of polymers on the physicochemical properties and biological performance of fenoprofen calcium dehydrate-triacetyl-β-cyclodextrin complex. Pharmaceutics. 2017;9(3):23. doi: 10.3390/pharmaceutics9030023, PMID: 28671624
19. Aparna C, Anusha M, Manisha B. Enhancement of dissolution of candesartan cilexetil. Asian J Pharm Clin Res. 2023;16(3):148-51. doi: 10.22159/Ajpcr.2023.V16i3.46626
20. Kar R, Mohapatra S, Bhanja S, Das D, Barik B. Formulation and *in vitro* characterization of xanthan gum-based sustained release matrix tablets of isosorbide-5-mononitrate. Iran J Pharm Res. 2010;9(1):13-9. PMID: 24363701
21. Soroush H, Ghorbani-Bidkorbeh F, Mortazavi SA, Mehramizi A. Formulation optimization and assessment of dexamethasone orally disintegrating tablets using box-Behnken design. Iran J Pharm Res. 2018;17(4):1150-63. PMID: 30568675
22. Alkhafaji SL, Alazawy RA, Mahood AM. Spectrophotometric determination of candesartan cilexetil and atenolol in pure and pharmaceutical forms. Int J Pharmacol Res. 2020;12(1):336-44. doi: 10.31838/ijpr/2020.12.01.059
23. Rane Y, Mashru R, Sankalia M, Sankalia J. Effect of hydrophilic swellable polymers on dissolution enhancement of carbamazepine solid dispersions studied using response surface methodology. AAPS PharmSciTech. 2007 Apr 6;8(2):27. doi: 10.1208/pt0802027, PMID: 17622105
24. Hoppe K, Sznitowska M. The effect of polysorbate 20 on solubility and stability of candesartan cilexetil in dissolution media. AAPS PharmSciTech. 2014;15(5):1116-25. doi: 10.1208/s12249-014-0109-8, PMID: 24871550
25. Saokham P, Muankaew C, Jansook P, Loftsson T. Solubility of cyclodextrins and drug/cyclodextrin complexes. Molecules. 2018 May 11;23(5):1161. doi: 10.3390/molecules23051161, PMID: 29751694