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DEVELOPMENT AND EVALUATION OF COMPRESSION COATED TIMED-RELEASE TABLETS OF CANDESARTAN CILEXETIL FOR CHRONOTHERAPY OF HYPERTENSION

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Candesartan Cilexetil, Anti-hypertensive, HPMC K15M, Eudragit S100, Compression coating, Chronotherapy, Timed-release, Solid dispersion

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ABSTRACT: Chronotherapy involves the release of drug to the systemic circulation based on the circadian rhythm associated with the pathophysiology of a disease. Candesartan Cilexetil, an anti-hypertensive drug, is formulated to contribute to the chronotherapy of hypertension. Solubility study of the drug (BCS Class II) in various media indicated maximum solubility in pH 6.8 sodium phosphate buffer containing 1% SLS. Solid dispersion of Candesartan Cilexetil with PVP K30 was prepared by melt dispersion. Core tablet containing solid dispersion equivalent to 16mg Candesartan Cilexetil was prepared by direct compression. The % dissolution efficiency (DE_{60}) of the pure drug was 31.05% and increased for the solid dispersion to 56%. Compression coating was applied to this core tablet by direct compression using release rate retardants HPMC K15M and Eudragit S100 in various proportions to give timed-release. *In-vitro* drug release test carried out in 0.1 N HCl for the first 2 h and pH 6.8 buffer containing 1% SLS for next 8 hrs showed formulation F4 containing 75 % of HPMC K15M and 25% Eudragit S100 as coat, to release only 5% drug in first 6 hrs, 85% release by 8th hr and 100% drug release by 10th h of study. Thus compression coated timed release tablets of Candesartan Cilexetil when administered at night will release the drug after 6 h lag time, *i.e.*, during the early morning hours when the blood pressure will be higher and contribute to chronotherapy of hypertension. F4 has been evaluated for stability for 2 months at 40°C/75%RH and was found to be stable.

INTRODUCTION: Candesartan Cilexetil, an anti-hypertensive drug, is an angiotensin II type 1 (AT1) receptor antagonist. It belongs to BCS class II. It is a prodrug which when administered orally is rapidly converted to Candesartan in the intestinal wall and has good absorption throughout the intestine. It has low oral bioavailability (15%) and a half-life of 9 h [1].

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Candesartan cilexetil is available as tablets of 4mg, 6mg, 8mg, 16mg, and 32mg. Hypertension is influenced by circadian rhythms. The blood pressure shows variation concerning day and night being lower during sleep time, rapidly rising during early morning/awakening and being highly variant during the awake period [2]. Chronotherapy involves the release of drug to the systemic circulation based on the circadian rhythm, associated with the pathophysiology of the disease [3]. Much work on Candesartan Cilexetil has been reported on solubility/bioavailability enhancement [4-10] and its sustained release [11-15].

The present work is aimed at formulating Candesartan Cilexetil tablets showing drug release

with a lag time of around 6 h followed by immediate release within 1 or 2 h, so that when administered at bedtime, the drug will be released during the early hours of the morning when the blood pressure will be higher and thus contribute to chronotherapy of hypertension.

MATERIALS AND METHODS:

Materials: Candesartan Cilexetil was a gift sample from Natco Pharma Ltd, Kothur, Hyderabad. Microcrystalline cellulose, lactose monohydrate, mannitol, sodium lauryl sulfate (SLS), ethylcellulose, Tween 20, Tween 80, magnesium stearate and talc were procured from SDFCL Mumbai; Polyvinylpyrrolidone K-30 and Eudragit S100 were procured from Oxford Laboratories, Mumbai; Croscarmellose sodium was procured from N R Chemicals Mumbai, HPMC E50 was procured from Loba Chemie, Mumbai and HPMC K15M was a gift sample from Taian Ruitai Cellulose Co. Ltd., Shandong Province, China.

Methods:

Analytical Method: A UV Spectrophotometric method based on measurement of absorbance at 254nm[4] in different media (pH 6.8 sodium phosphate buffer containing 1% w/v SLS; SLS - 0.5%, 0.75%, and 1% w/v; phosphate buffers pH - 6.4, 6.8 and 7.2; Tween-20 - 0.15%, 0.35% and 0.55% w/v; Tween-80 - 0.1%, 0.3% and 0.5% w/v; 0.1N HCl, distilled water) was used for the estimation of Candesartan Cilexetil. From 1mg/ml methanolic stock solution of the drug, series of dilutions containing 2, 4, 6, 8 and 10 µg/ml of Candesartan Cilexetil was each prepared in the respective media listed above. The absorbance of these solutions was measured against the respective media as blank at 254nm using U.V-Visible double beam spectrometer Elico SL191 (n=3). The method was validated for linearity, accuracy, and precision.

Solubility Studies: The saturation solubility of Candesartan Cilexetil was determined in various buffers and surfactant solutions by shake flask method [6].

Excess amount of drug was added to each ampoule containing 5ml of medium (n=3).

The ampoules were sealed and placed suitably in an orbital shaker (Orchid Scientifics CS/05) and maintained at 150 rpm and 30 ºC for 48 h. The ampoules were then equilibrated for 24 h. Each ampoule contained a clear supernatant liquid and sediment. The tip was carefully broken, and the clear supernatant liquid was collected and centrifuged. Aliquots of this supernatant were diluted with respective media and estimated for drug UV- spectrophotometrically**.**

Preparation of Solid Dispersion by melt dispersion: Solid dispersions of drug with PVP K30 were prepared by melt dispersion [6] method with different ratios of the drug: carrier (1:1, 1:2, 1:3, 2:1, 3:1, 4:1, 2:3). Drug and carrier were accurately weighed and transferred to china dish. The contents were gently heated to a temperature just beyond the melting point of drug and carrier to give a molten mass. The melt was rapidly cooled by placing it in an ice bath. The solidified mass was pulverized and passed through sieve 60.

Solubility study of Solid Dispersion: The water solubility of solid dispersions was determined by shake flask method described above (n=3). The solid dispersion which showed higher water solubility would be used in the preparation of core tablets.

DSC study of Solid Dispersion: Thermal investigations of solid dispersions were performed by using Perkin Elmer scanning calorimeter. In an aluminum pan, 2-3mg of the sample (pure drug/ solid dispersion) was placed and crimped with a lid containing a pinhole and kept in the DSC unit. A blank pan was used as a reference. The sample was heated at 10 ºC/min from a temperature range of 120-250 ºC under nitrogen flow, and the thermogram was generated.

Drug Content of Solid Dispersion: Solid dispersion equivalent to 16 mg Candesartan Cilexetil was accurately weighed and dissolved in methanol. Further dilutions were made with pH 6.8 sodium phosphate buffer containing 1% SLS and then analyzed for drug content and expressed as % of theoretical drug content (n=3).

Preparation of Immediate Release Core Tablet: Core tablet was prepared by incorporating optimized solid dispersion at a dose equivalent to 16mg Candesartan Cilexetil by direct compression as per the formulae are given in **Table 1**. The powder blend for core tablet was studied for the

pre-compression parameters like angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index, (n=5). Drug / solid dispersion and excipients (except lubricant) were weighed accurately and blended in geometrical proportions in a mortar. The lubricant was then added to the powder and blended. The resultant blend was directly compressed to tablets using 6mm round flat-faced punches using Rimek eight-station rotary compression machine. The tablets were further evaluated.

TABLE 1: FORMULATION OF CORE TABLET

Composition (mg/tablet)	IC1	IC2	IC3	IC4	IC5
16 mg Drug equivalent	Pure drug - 16	SD1- 32	SD7- 40	SD1- 32	SD7 - 40
Microcrystalline cellulose	27.5	11.5	3.5	-	-
Lactose monohydrate	-	-	-	11.5	3.5
Crosscarmellose sodium	5	5	5	5	5
Magnesium stearate	1	1	1	1	1
Talc	0.5	0.5	0.5	0.5	0.5
Weight of tablet	50	50	50	50	50

Drug: carrier SD1- 1:1, SD7- 2:3

Assay: The core tablet was crushed to a fine powder. The contents were added to a 10ml volumetric flask containing 2-3 ml methanol. The contents were sonicated. The clear solution obtained was made up to the mark with methanol. Suitable dilutions were made with pH 6.8 sodium phosphate buffer containing 1% SLS and estimated for drug content spectrophotometrically.

Uniformity of Content: [16] As the dose of the drug is low, the content uniformity test is performed. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Not less than 30 units are selected. 10 units are assayed individually, and the accepted value is calculated. If the acceptance value is not acceptable, another 20 tablets are assayed, and acceptance value is calculated.

$$\text{Acceptance Value (AV)} = \left|M-\overline{X}\right| + ks$$

Where, $\overline{X}$ = Mean of individual contents (x_1, x_2,…., x_n), expressed as a percentage of the label claim.

x_1, x_2,…., x_n Individual contents of the units tested, expressed as a percentage of the label claim.

n Sample size (number of units in a sample)

k = acceptability constant; if n=10, k = 2.4; if n = 30, k = 2.0

s = sample standard deviation calculated as;

$$\left[\frac{\sum_{i=1}^{n}(x_i-\overline{X})^2}{n-1}\right]^{\frac{1}{2}}$$

T = Target content per dosage unit at the time of manufacture expressed as a percentage of the label claim. Unless otherwise stated, T is 100.0 percent, or T is the manufacturer's approved target content per dosage unit.

M (case 1) to be applied when T ≤101.5

If 98.5% ≤ $\overline{X}$ ≤ 101.5%, then M = $\overline{X}$ and (AV = ks)

If $\overline{X}$ <98.5%, then M = 98.5%; (AV = 98.5 – $\overline{X}$ + ks)

If $\overline{X}$ >101.5%, then M = 101.5%; (AV = $\overline{X}$ – 101.5 + ks)

M (case 2) to be applied when T >101.5

If 98.5 ≤ $\overline{X}$ ≤T, then M = $\overline{X}$; (AV = ks)

If $\overline{X}$ <98.5%, then M = 98.5%; (AV = 98.5 – $\overline{X}$ + ks)

If $\overline{X}$ >T, then M=T%; (AV = $\overline{X}$ – T + ks)

L1 = Maximum allowed acceptance value; L1 = 15.0 unless otherwise specified

L2 = Maximum allowed range for deviation of each dosage unit tested from the calculated value of M. L2 = 25.0 unless otherwise specified.

On the low side, no dosage unit result can be less than [1–(0.01)(L2)]M, while on the high side no dosage unit result can be greater than [1 +(0.01)(L2)]M. (This is based on an L2 value of 25).

Friability: Pre-weighed sample of tablets equal to 6.5g were placed in a friabilator (Electrolab), which was then operated for 100 revolutions. Tablets were dusted and reweighed. % friability is given as

$$\% F = (W_o - W) \times 100 / W_o$$

Where W_o is the weight of the tablets before the test, and W is the weight of the tablets after the test.

Thickness and Hardness of the Core Tablet: Tablet thickness was measured by using a calibrated screw gauge (n=10). Tablet hardness was measured by Monsanto hardness tester (n=10).

Disintegration Test of Core Tablet: The disintegration time of the tablets was determined using the Electrolab ED-2AL disintegration test apparatus. The immersion fluid was maintained at 37 °C. One tablet each was added to the tubes of the basket rack assembly, and the time taken for the complete disintegration was observed. The test was carried out in pH 6.8 sodium phosphate buffer containing 1% SLS.

***In-vitro* Dissolution Study of Core Tablet:** The *in-vitro* dissolution study of Candesartan cilexetil core tablets was carried out using Electrolab TDT14L fourteen station dissolution test apparatus in 900ml of pH 6.8 sodium phosphate buffer containing 1% SLS maintained at 37 ± 0.5 ºC with paddle stirrer at 50 rpm. One tablet each was added to the dissolution vessel, and the study was carried out for 1 h. At regular intervals of 10 min, 5 ml samples of dissolution medium were withdrawn and filtered through the 0.45 µm filter.

5 ml of fresh medium was replaced immediately. The samples were estimated against the respective media as blank at 254 nm. Correction factor for loss of drug during sampling was included in the calculation since the dose is low. (n=3)

Preparation of Compression Coated Tablets: The dry coat was formulated using various proportions of HPMC and EC as given in **Table 2.** The coat material powder blend was subjected to evaluation for bulk and tapped densities, angle of repose, Carr's index, and Hausner's ratio. 10 mm round flat plain punches were selected to prepare compression coated tablets. Half the quantity of the coat material powder blend was placed in the die cavity. The core tablet (6 mm diameter, 2 mm thickness) was carefully placed in the center of the die cavity, filled with the other half of the coating material and compressed.

TABLE 2: FORMULATION OF COMPRESSION COATED TABLETS

Ingredients (mg/tablet)	F1	F2	F3	F4	F5
Core tablet (50 mg)	IC4	IC4	IC5	IC5	IC5
HPMC E 50M	50	50	-	-	-
HPMC K15M	-	-	150	200	225
EC	250	-	-	-	-
Eudragit S100	-	250	150	100	75
Tablet weight (mg)	400	400	400	400	400

Evaluation of Compression Coated Tablets: The compression coated tablets were evaluated for hardness, friability, and thickness as described earlier. Disintegration test was carried out in 0.1NHCl as well as pH 6.8 sodium phosphate buffer containing 1% SLS. Content uniformity test for the core tablet was considered for the compression coated tablets, and the test was not repeated.

Swelling Study: Swelling studies of compression coated tablets were carried out in two media for 10 h. Accurately weighed tablets were initially placed in 20ml 0.1N HCl taken in a petri dish. At 1 h intervals of time, each tablet was wiped gently with tissue paper and weighed. After 2 h, the tablets were transferred to 20 ml of pH 6.8 sodium phosphate buffer, and the tablet weight was recorded at hourly intervals.

The swelling index concerning time is calculated according to the formula:

$$\text{Swelling index} = Ws - Wi \times 100 / Wi$$

Where Wi is the initial weight of the tablet, Ws is the weight of the swollen tablet.

***In-vitro* Drug Release Study of Compression Coated Tablet:** The *in-vitro* drug release study of Candesartan cilexetil compression coated tablets was carried out using Electrolab TDT 14L fourteen station dissolution test apparatus with paddle stirrer at 50 rpm in 900 ml 0.1N HCl for first 2 hours followed by pH 6.8 sodium phosphate buffer containing 1% SLS for the next 10 h. The medium was maintained at 37 ± 0.5 ºC. One tablet each (n=3) was added to the dissolution vessel and study carried out. 5 ml samples were withdrawn through

the filter at hourly time intervals, and fresh medium was replaced in the dissolution vessel. The samples were estimated against the respective media as blank at 254 nm. Correction factor for loss of drug during sampling was included in the calculation since the dose is low. The data were treated according to zero-order, first-order, Higuchi, and Peppas equation models.

Preliminary Stability Study of Selected Formulation: The optimized compression coated tablet F4 was subjected to stability study at 40 ± 2 ºC and 75 ± 2% RH for a period of two months in Newtronics NEC 204 ETS humidity chamber. The tablets were wrapped in an aluminum foil for storage. Samples were taken at monthly intervals and analyzed for appearance, drug content, and *in-vitro* drug release.

RESULTS AND DISCUSSION:

Analytical Method: The standard curves were constructed in various media and the method was found to be linear and mostly precise as indicated by the correlation coefficient 'r' values and low % CV values given in **Table 3**.

Solubility Study: Since Candesartan Cilexetil is an insoluble drug, solubility study was carried out in surfactants and buffers as given in **Table 4**. pH 6.8 sodium phosphate buffer containing 1% SLS showed highest drug solubility and was selected as dissolution medium.

Preparation and Evaluation of Solid Dispersion of Candesartan Cilexetil: Solid dispersions of Candesartan Cilexetil with PVP K30 were successfully be prepared by melt dispersion method with different ratios of the drug: carrier. From the DSC thermograms given in **Fig. 1A, 1B** and **1C** Candesartan cilexetil exhibited a single endothermic peak onset at 168 ºC corresponding to the melting point of the drug. The thermogram of solid dispersions SD1 and SD7 indicated the disappearance of the peak. It could be attributed to the destruction of the crystal lattice, because of the conversion of the drug into amorphous form in the solid dispersion. From **Table 5,** drug content of the solid dispersions was found to be in the range of 94.2-99.1% w/w indicating that the drug is completely incorporated into the carrier. The solubility of all the solid dispersions in water is higher than that of pure drug. SD7 and SD1 showed higher water solubility. These solid dispersions were selected to prepare a core tablet.

TABLE 3: CHARACTERISTICS OF STANDARD CURVE OF CANDESARTAN CILEXETIL IN VARIOUS MEDIA AT 254nm UV SPECTROPHOTOMETRICALLY

Medium	r	%CV range
6.8 pH sodium phosphate buffer with 1% SLS	0.996	0.49 - 2.7
0.1NHCl	0.99	0.5 - 2.3
Water	0.99	0.84 - 2.3
0.5%SLS	0.987	2.6 - 8
0.75%SLS	0.99	0.2 - 8
1%SLS	0.989	0.8 - 3.1
0.1% Tween 80	0.99	0.4 - 2.08
0.3% Tween 80	0.99	0.6 - 7.8
0.5% Tween 80	0.987	0.4 - 2.08
0.15% Tween 20	0.987	0.14 - 3.3
0.35% Tween 20	0.972	0.2 - 3
0.55% Tween 20	0.951	0.49 - 2.7
pH 6.4 buffer	0.986	0.3 - 2.9
pH 6.8 buffer	0.974	0.7 - 2.8
pH 7.2 buffer	0.987	0.01 - 2.6

TABLE 4: SOLUBILITY OF CANDESARTAN CILEXETIL IN VARIOUS MEDIA

Medium		Solubility(n=3) µg/ml x ± sd
Water	-	4.47 ± 0.01
SLS	1%	24.13 ± 0.02
	0.75%	20.58 ± 1.20
	0.50%	21.71 ± 0.01
Buffers	7.2 pH	0.91 ± 0.06
	6.8 pH	1.02 ± 0.08
	6.4 pH	0.85 ± 0.06
Tween-20	0.55%	1.714 ± 0.09
	0.35%	2.27 ± 0.07
	0.15%	0.85 ± 0.05
Tween-80	0.50%	4.70 ± 0.07
	0.30%	2.51 ± 0.06
	0.10%	0.40 ± 0.09
pH 6.8 containing 1% SLS	-	32.14 ± 0.04

TABLE 5: CHARACTERISTICS OF CANDESARTAN CILEXETIL SOLID DISPERSIONS

Code	Drug : carrier	Water solubility (µg/ml) x ± sd	Drug content (%) x ± sd
Pure drug	-	4.47 ± 0.01	-
SD1	1:1	7.37 ± 1.22	98.2 ± 0.02
SD2	1:2	4.69 ± 0.99	96.4 ± 0.04
SD3	1:3	3.98 ± 1.43	96.6 ± 0.08
SD4	2:1	6.81 ± 1.33	94.2 ± 0.06
SD5	3:1	6.37 ± 1.20	97.2 ± 0.02
SD6	4:1	6.67 ± 1.10	98.2 ± 0.06
SD7	2:3	11.54 ± 1.44	99.1 ± 0.02

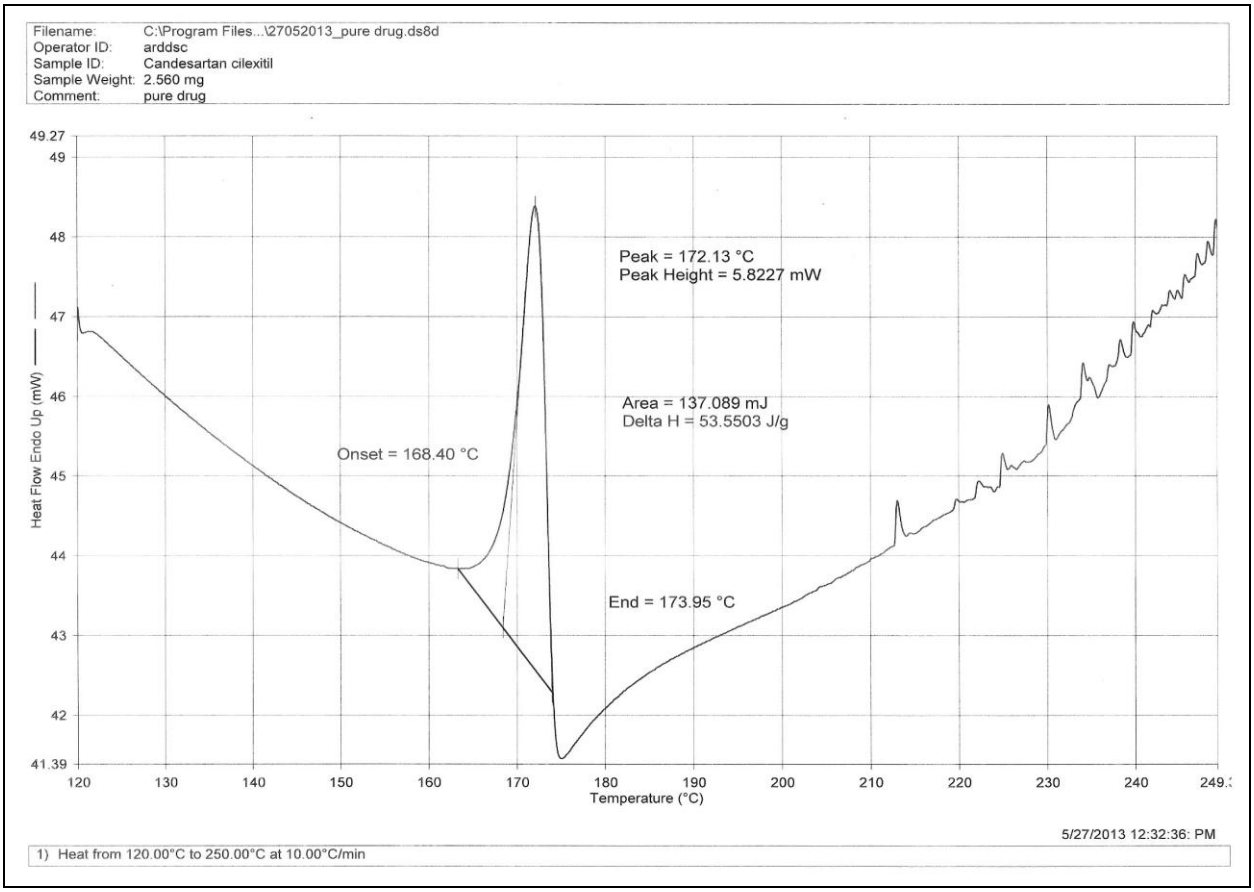

FIG. 1A: DSC THERMOGRAM OF CANDESARTAN CILEXETIL

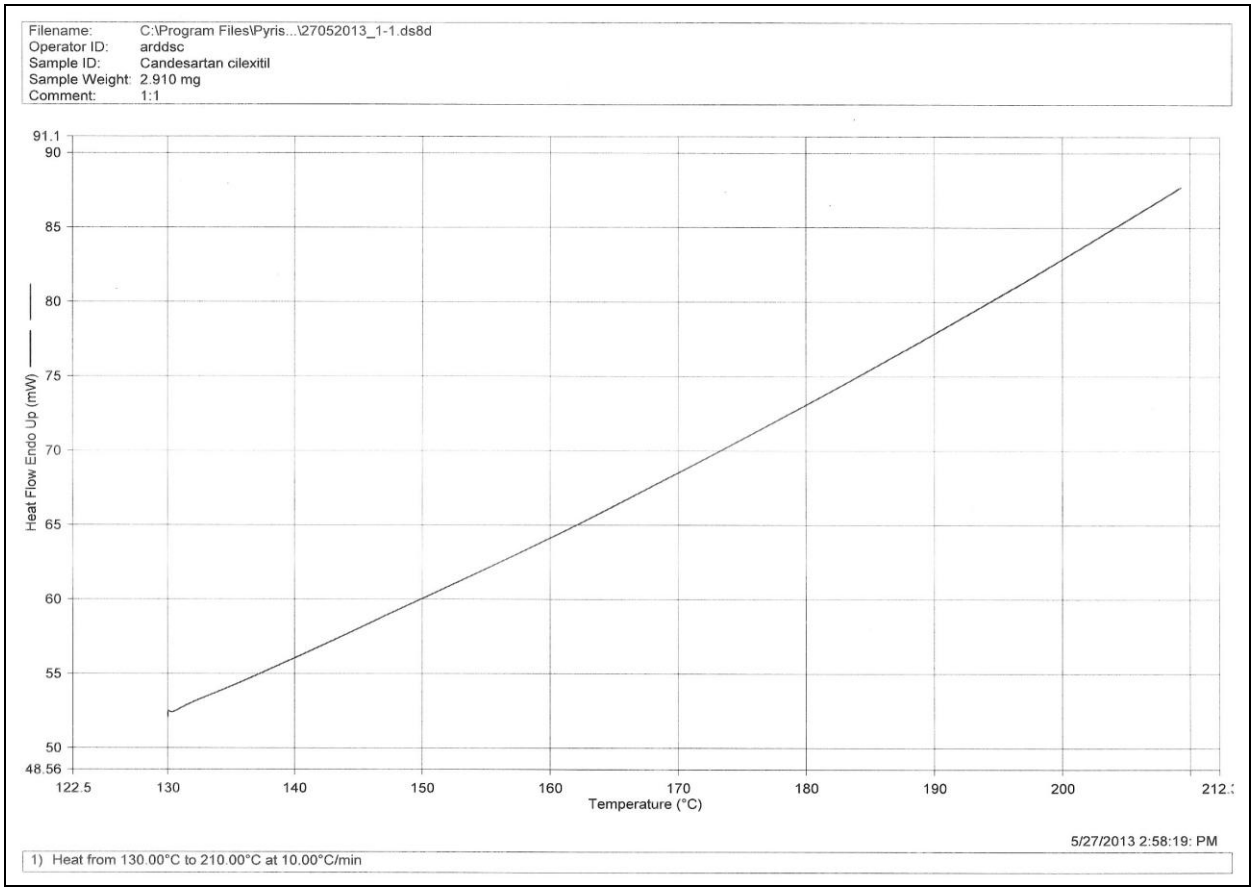

FIG. 1B: DSC THERMOGRAM OF SD1

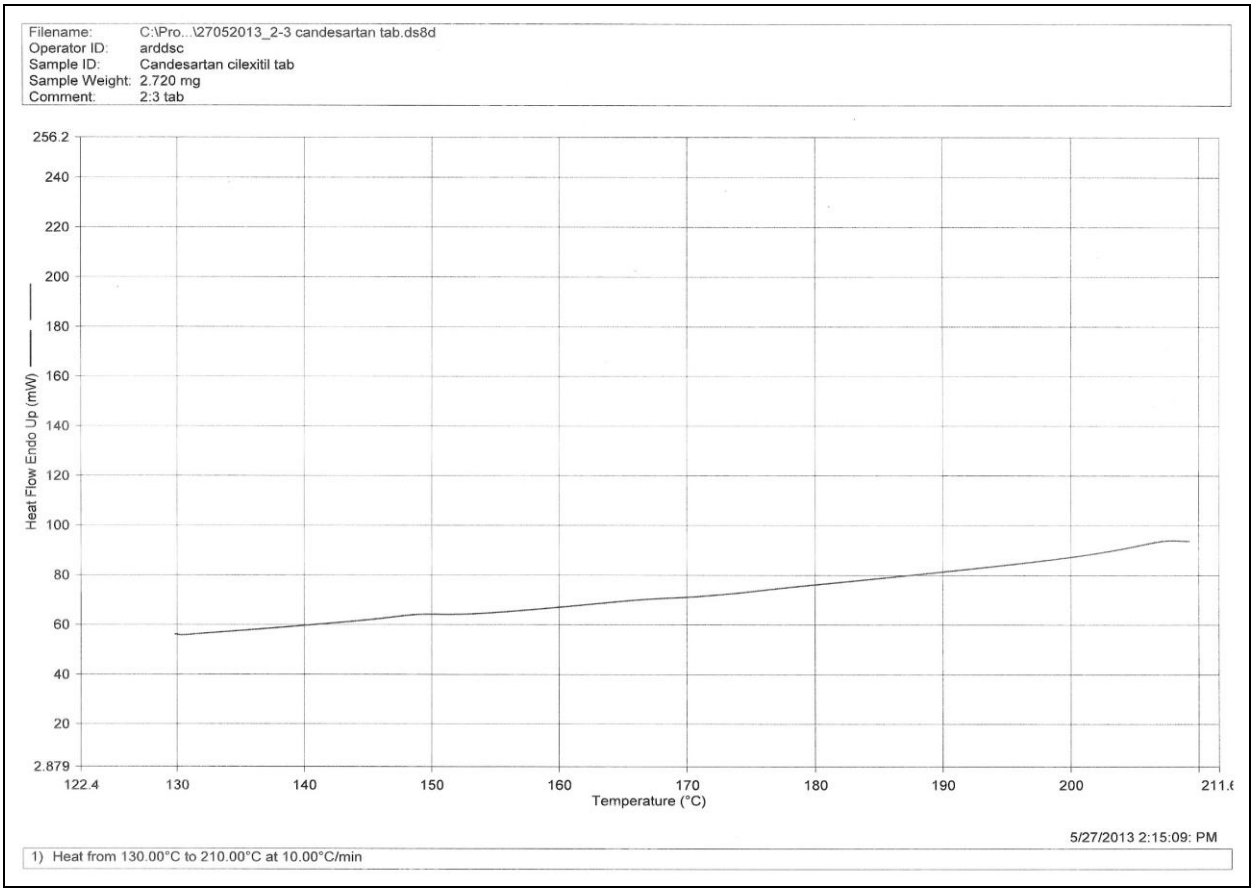

FIG. 1C: DSC THERMOGRAM OF SD7

Preparation and Evaluation of Core Tablet of Candesartan Cilexetil: Core tablets were prepared according to the formula given in **Table 1**. Precompression properties of core material blend given in **Table 6** indicate good to passable flow properties and good compressibility. Tablets were prepared by direct compression.

The tablet characteristics given in **Table 7** indicate achievement of content uniformity as the acceptance value (AV) is less than 15. The disintegration time of all the tablets is within 5-6 min, meeting the requirements for immediate release. *In-vitro* dissolution profile of the core tablets given in **Figure 2** indicate that the core tablets IC4 and IC5 showed maximum dissolution 97.15% and 100.1% respectively within 60 minutes.

From **Table 8**, the R^2 value for both IC4 and IC5 was higher for the zero-order kinetic model (0.99) than the first-order model (0.82 and 0.85) respectively. The release rates of IC4 and IC5 (1.6mg/min) were found to be three times higher than that of IC1 (0.52mg/min) containing the pure drug. The % DE_{60} values were higher (56%) for tablet containing solid dispersion than that containing pure drug (31.05%). The R^2 value for all core tablets for Hixson Crowell model is around 0.91, which suggests that the dissolution proceeded by surface reduction.

TABLE 6: PRECOMPRESSION PARAMETERS OF CORE MATERIAL

Core tablet	Angle of repose	Bulk Density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Compressibility index (%)
IC1	24.10	0.161	0.212	1.24	21.02
IC2	24.45	0.159	0.218	1.21	21.04
IC3	23.6	0.169	0.223	1.31	24.22
IC4	24.03	0.165	0.225	1.30	22.41
IC5	25.05	0.171	0.242	1.29	25.4

TABLE 7: CORE TABLET CHARACTERISTICS

Core tablet	Assay x ± sd (n=10)	Content uniformity AV*	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (min)
IC1	96.25 ± 1.744	9.41	1.56 ± 0.09	1.99 ± 0.04	0.71 ± 0.06	6 ± 0.032
IC2	96.24 ± 1.432	7.76	1.75 ± 0.02	2.01 ± 0.05	0.64 ± 0.08	6 ± 0.02
IC3	96.71 ± 1.616	6.94	2.51 ± 0.06	2.14 ± 0.08	0.74 ± 0.09	5 ± 0.04
IC4	96.4 ± 1.783	8.76	2.65 ± 0.08	2.22 ± 0.09	0.61 ± 0.05	5.5 ± 0.02
IC5	97.25 ± 1.904	5.71	2.45 ± 0.04	2.51 ± 0.04	0.59 ± 0.03	5 ± 0.04

*Acceptance value

TABLE 8: DISSOLUTION CHARACTERISTICS OF CORE TABLET

Code	Zero order R^2	K_0 (mg/min)	First order R^2	K_1 (min^{-1})	Hixson Crowell R^2	K_{HC} ($mg^{1/3}$ min^{-1})	t_{90} (min)	% DE_{60}
IC1	0.884	0.527	0.922	0.0046	0.971	0.008	-	31.05
IC2	0.957	0.986	0.942	0.0163	0.956	0.011	-	35
IC3	0.947	0.811	0.969	0.0114	0.921	0.005	-	23.7
IC4	0.996	1.660	0.819	0.0503	0.907	0.026	54.5	54
IC5	0.998	1.680	0.849	0.0341	0.914	0.035	52.5	56

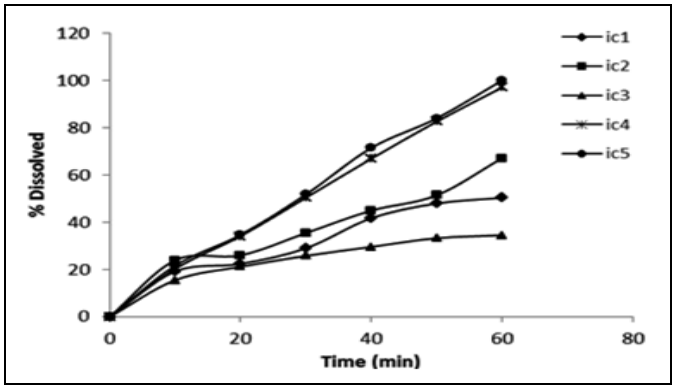

FIG. 2: % DISSOLVED *VS.* TIME PROFILE OF CORE TABLET

Preparation and Evaluation of Compression Coated Tablet of Candesartan Cilexetil: As per the formulae are given in **Table 2,** compression coated tablets could successfully be prepared without chipping, cracking, or lamination problems by direct compression. The pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio as given in **Table 9** for all formulation blends showed that the blends were free-flowing and had good compressibility. The prepared compression coated tablets were evaluated for hardness, thickness, friability, and disintegration time, and the data is given in **Table 10.**

Hardness was in the range of 5-6 kg/cm^2, the thickness was around 5mm and % friability was also less than 1%. Disintegration time was more than 6 h in both the media (0.1NHCl and pH6.8 buffer with 1%SLS) indicating the suitability of compression coated tablets for timed release.

TABLE 9: PRECOMPRESSION PARAMETERS OF COAT MATERIAL WITHOUT CORE TABLET

	Angle of repose	Bulk Density (g/ml)	Tapped density (g/ml)	Hausner's ratio	% Compressibility index
F1	26.01	0.208	0.594	1.16	15.49
F2	26.38	0.234	0.694	1.19	14.35
F3	22.12	1.24	1.19	1.20	16.77
F4	27.01	0.276	0.609	1.83	16.08
F5	28.46	0.274	0.621	1.18	15.43

TABLE 10: CHARACTERISTICS OF COMPRESSION COATED TABLETS

Tablet	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (h)
F1	5.50 ± 0.09	5.32 ± 0.04	0.63 ± 0.06	> 6 in
F2	5.6 ± 0.06	5.41 ± 0.02	0.45 ± 0.03	0.1NHCL
F3	5.85 ± 0.02	5.11 ± 0.03	0.45 ± 0.05	and
F4	6.51 ± 0.05	5.56 ± 0.08	0.43 ± 0.06	pH 6.8 buffer with 1%SLS
F5	6.11 ± 0.08	5.33 ± 0.06	0.44 ± 0.08	

Swelling Studies: Swelling studies for the compression coated tablets given in **Table 11** indicate that F1 and F2 formulae did not show much variation in percent swelling as low viscous

grade HPMC E50M has been employed. F3, F4, and F5 formulae showed a significant increase in percent swelling as high viscous grade HPMC K 15M has been used. As the proportion of HPMC K 15M increased, the % swelling has been increased. After maximal swelling, reduction in weight is observed, which may be due to slow erosion or dissolution of HPMC.

TABLE 11: SWELLING STUDY OF COMPRESSION COATED TABLETS

Time (h)	% Weight gained on swelling				
	F1	F2	F3	F4	F5
1	4.62	5.62	57.8	60.4	68.7
2	8.98	9.41	80.5	94.3	100.4
3	12.72	12.5	91.5	115.9	131.4
4	15.79	15.75	120	132	160.3
5	18.75	16.07	156	171	77.9
6	20.82	23.76	119	78.9	34.8
7	22.48	26.36	89.8	8.26	-
8	12.67	10.61	-10.2	-17.9	-
9	5.6	6.69	-19.7	-	-
10	0.56	1.21	-	-	-

***In-vitro* Drug Release Study of Compression Coated Tablets of Candesartan Cilexetil:** From the drug release profiles of compression coated tablets given in **Fig. 3**, it can be observed that % drug release varied from 55.98% to 99.98% after 10 hrs of study. Two hours lag time was observed with F1 and F2, which may be attributed to employing of low viscous grade HPMC E50. The sustained-release pattern was observed, and it is primarily due to the effect of rate-controlling polymers EC (insoluble at all pH range) and Eudragit S100 (soluble above pH 7) incorporated in F1, F2, respectively rather than low swelling HPMC E50.

Formula F3 showed a lag time of 6hrs where only 3.6% has been released. Subsequently, a sustained release pattern was observed when equal proportions of HPMC K 15M and Eudragit S100 were employed here. The tablet F3 on observation during dissolution study was found to erode into particles after 9th h by swelling study given in **Table 11**. Until then, the tablet was in intact. With F4 also only 3.6% drug release was observed in the first 6 h, indicating an achievement of desired lag time. 85% drug release was achieved within next 2 hrs, *i.e.* 8th h and complete drug release was obtained by 10th h. The swelling index of F4 indicates that tablet started eroding after 7th h. The compression coating comprised a swellable polymer HPMC K 15M and non-swellable or insoluble Eudragit S100 which causes only partial swelling of the compression coating.

Occupation of interstitial spaces of HPMC K 15M by Eudragit S 100 leads to detachment and erosion of swollen HPMC K 15M layer as observed. F5 showed only 4 h lag time and complete drug release in next 2 h. This is due to the higher proportion of HPMC K15M, which led to rapid swelling. The swelling study also showed that the tablet was intact up to 4 h and started eroding.

The characteristics of drug release study given in **Table 12** indicate higher R^2 value (0.9 to .98) for the zero-order model than for first-order model (0.5 to 0.84). Hence drug release follows zero-order kinetics. Higuchi model suggests drug release by diffusion from the swollen polymeric system. The mechanisms of drug release as per the Peppas model showed good correlation as R^2 values were in the range of 0.93–0.97. 'n' value for F4 and F5 indicates the super case-II mechanism of drug release that depends on swelling, relaxation, and erosion of the polymer. F4 shows the ideal release profile for achieving the timed release of Candesartan Cilexetil suitable for chronotherapy.

TABLE 12: DRUG RELEASE CHARACTERISTICS OF COMPRESSION COATED TABLETS

	Zero order R^2	K_0 (mgh^{-1})	First order R^2	K_1 (h^{-1})	Higuchi R^2	K_h ($mgh^{-1/2}$)	Peppas R^2	n	t_{10} (h)	t_{50} (h)	t_{90} (h)
F1	0.949	5.56	0.843	0.75	0.851	17.36	0.946	0.346	3	9.4	-
F2	0.943	3.106	0.847	0.31	0.844	9.65	0.977	0.734	5.5	-	-
F3	0.900	10.79	0.847	0.018	0.801	5.381	0.959	2.324	6.2	-	-
F4	0.980	9.207	0.504	0.034	0.921	26.40	0.936	2.79	6	8.3	8.9
F5	0.988	15.23	0.535	0.075	0.939	35.97	0.960	2.101	4	5.5	6

Preliminary Stability Studies: The optimized tablets of formulation F4 were kept for stability studies. There was no change in physical appearance, color. Formulations were analyzed at the end of 1st and 2nd months for the assay and dissolution studies. Drug content of the tablets was

found to be 95.5 ± 0.6%. *In-vitro* dissolution profile given in **Fig. 4** showed that there was no significant change in the release profile of the drug from optimized tablets at the end of 2 months. The mean dissolution time was evaluated by two-tailed paired t-test at $p < 0.05$ and 2 degrees of freedom. The calculated value of 0.18 is less than the table value 4.3, indicating no significant difference in the mean dissolution time and that the formulation is stable.

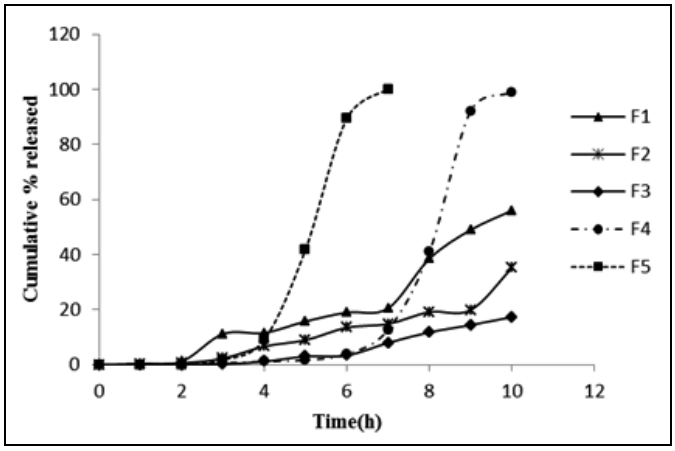

FIG. 3: DRUG RELEASE PROFILE OF COMPRESSION COATED TABLETS

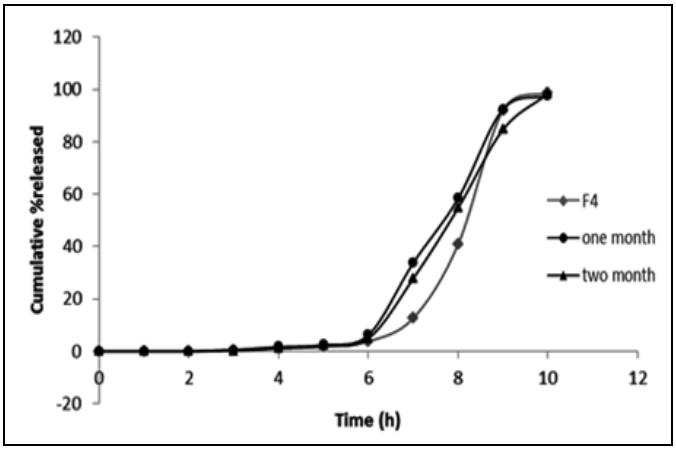

FIG. 4: DRUG RELEASE PROFILE AFTER STABILITY STUDY

CONCLUSION: Stable, timed-release tablets of Candesartan cilexetil could be successfully prepared by compression coating technique. The release profile with a lag time of 6 h and 100% release within next 1-2 h indicates the suitability of the formulation for the chronotherapy of hypertension where the tablet, when taken at bed time, would release the drug in early hours of the morning leading to desired therapeutic effect.

Future prospective includes *in-vitro* dissolution study in a bio relevant media and *in-vivo* studies for the optimized formula to predict the actual release behavior. The optimized formula may be modified by compression coating technique to achieve once daily pulsed release chronotherapeutic drug delivery system for candesartan cilexetil. The compression coating technique may be extended to other antihypertensive agents and other diseases where chronotherapy may be beneficial.

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