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FORMULATION AND EVALUATION OF SUBLINGUAL TABLET OF CANDESARTAN CILEXETIL

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Abstract: Candesartan Cilexetil is a non-peptide angiotensin II type-1 (AT1) receptor antagonist used in the treatment of Hypertention, Congestive heart failure and myocardial infarction. It comes under the class-II of the BCS system whose bioavailability is 15%. The present investigation was undertaken to enhance solubility of Candesartan Cilexetil and to formulate sublingual tablet of Candesartan Cilkexetil. Phase solubility study was performed to enhance solubility of drug. The solid dispersion of the Candesartan Cilexetil were prepared with β-cyclodextrin and PVP K-30 in various ratio and solubility was performed. Solid dispersions were prepared by kneading method. The optimized solid dispersion was used for preparation of sublingual tablet. The tablets were made using different superdisinegrants like crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG) by direct compression method and evaluated for hardness, weight variation, friability, disintegration time, wetting time, drug content, In- vitro drug release and *Ex vivo* permeation study. Short term stability study of optimized formulation was performed as per ICH guideline Q1C for 1 month. β-cyclodextrin in molar ratio 1:2 showed profound effect on solubility. So, Drug+β-cyclodextrin complex in 1:2 molar ratio was selected for further study. The optimized formulation (F9) containing 5% Crospovidone, 30% Mannitol showed less friability, less Disintegration time 10.67±1.03 and more than 90% drug release within 15 min. Stability study of the optimized formulation showed that formulation was stable.

Keywords: Sublingual tablet, Candesartan Cilexetil, Phase solubility study, β-cyclodextrin, Crospovidone

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INTRODUCTION

Sublingual administration of the drug means placement of the drug 'under the tongue' and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained into systemic circulation. [1]

Sublingual route provides systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation. Systemic drug delivery provide immediate onset of pharmacological effect through the sublingual route. [2]

Drugs having short delivery and infrequent dosing regimen could be delivered successfully through sublingual route because of high permeability and rich blood supply, the sublingual route produces a rapid onset of action. [3]

Candesartan Cilexetil is an ester prodrug. Candesartan Cilexetil is chemically 2-ethoxy-3-[21-(1*H*-tetrazol-5-yl) biphenyl-4 ylmethyl]-3*H*-benzoimiadazole-4-carboxylic acid 1 cyclohexyloxycarbonyloxy ethyl ester with chemical formula $C_{33}H_{34}N_6O_6$ and molecular weight 610.67. It is white to off-white powder with melting point 157-160° C.[4]

Candesartan Cilexetil (CC) is a selective AT1 subtype angiotensin II receptor antagonist and candesartan acts by blocking the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues such as vascular smooth muscle and the adrenal gland. Candesartan is widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy.[4] [5]

Candesartan Cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to Candesartan.[4]

Half life of the Candesartan Cilexetil is 5.1 to 10.5 hrs.[6] Following administration of Candesartan Cilexetil, the absolute bioavailability of Candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (Cmax) is reached after 3 to 4 hours. Food with a high fat content has no affect on the bioavailability of Candesartan from Candesartan Cilexetil.[7]

Candesartan Cilexetil is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration.[8]

Sublingual route gives the better alternative and more reliable in the terms of....

- Avoidance of first pass effect
- Provide fast dissolution and disintegration in oral cavity without need of water
- Onset of action
- Improved patient compliance

Advantages of Sublingual Tablet.... [1] [9-10]

- Drug is directly entered into systemic circulation so there is no loss of drug by first pass effect.
- Higher bioavailability and onset of action compare to oral route.
- Rapid absorption due to high vascularization beneath the tongue.
- Provide fast dissolution or disintegration in oral cavity without water or chewing action.
- Relatively large contact surface area provides rapid and extensive absorption
- Ease of administration to patients
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma, angina.
- pH in the mouth is relatively neutral so drug will be more stable.
- Less variability in therapeutic effect, more predictable pharmacokinetics
- Optimal effect achieved with less drugs, less side effects
- Improved patient compliance.

The aim of this study is to enhance the solubility of Candesartan Cilexetil and formulate evaluate sublingual tablet of Candesartan Cilexetil

MATERIAL AND METHOD:

Candesartan Cilexetil was obtained as a gift sample from Alembic Pharmaceuticals Ltd., Baroda, India. PVP K-30 was supplied from Yarrow chem., Mumbai, India. β-cyclodextrin was supplied by Yarrow chem., Mumbai, India. India. Cross PVP, Sodium starch glycolate, Croscarmellose

sodium were supplied by Yarrow chem., Mumbai, India. All other materials used were of pharmaceutical or analytical grade.

Differential Scanning Calorimetry (DSC) study

Differential Scanning Calorimeter study of thr Candesartan Cilexetil and Candesartan Cilexetil+ β-cyclodextrin was carried out using Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) instrument.

FTIR spectrophotometric study

Fourier transform infrared (FTIR) technique was used to study the physical and chemical interaction between drug and excipients used. The infrared spectrum of the native drug Candesartan Cilexetil and mixture of Candesartan Cilexetil and excipients were recorded in the range of 4000-400cm^{-1} using KBr mixing method on FTIR instrument.

(FTIR-8400S, Shimadzu, Kyoto, Japan).

Phase Solubility Study

The physical mixtures of drug (50 mg) and carrier as per specified drug:carrier ratio was added to vial containing 10 ml of phosphate buffer 6.8 pH and subjected to shaking on a rotary shaker for 48 hours at 37°C. Then the flasks were removed and content was filtered by 0.45μm membrane filter paper and analyzed for the drug content after appropriate dilution with phosphate buffer 6.8 pH and compared with pure drug solubility.

Table 1: Physical mixture of drug with different carriers

Sr. No.	Carrier	Ratio
1.	PEG 4000	1:1
2.	PEG 6000	1:1
3.	PVP K-30	1:1
4.	Poloxamer 188	1:1
5.	Poloxamer 407	1:1
6.	PVA	1:1
7.	β-cyclodextrin	1:0.5 (Molar ratio)

Table 2: Physical mixture of Drug with PVP K-30 and β-cyclodextrin

Sr. No.	Carrier	Ratio
1	PVP K-30	1:1
		1:2
		1:3
		1:4
2.	β-cyclodextrin (Molar ratio)	1:0.5
		1:1
		1:1.5
		1:2

Preperation of solid dispersion by kneading technique

Solid dispersion prepared by using a different ratio of drug with PVP K-30 and β-cyclodextrin. β-cyclodextrin was taken in mortar and 50% ethanolic aqueos solution was added and titurated to get slurry then drug slowly incorporated in to slurry and triturated for 1 hour. Slurry was air dried for 24 hours, Pulverized pass through sieve no. 60 and evaluated for solubility.

Table 3: Solid dispersion of drug with PVP K-30 and β-cyclodextrin

Sr. No.	Carrier	Ratio
1	PVP K-30	1:1
		1:2
		1:3
		1:4
2.	β-cyclodextrin (Molar ratio)	1:0.5
		1:1
		1:1.5
		1:2

Ternery solid dispersion of drug with PVP K-30 and Poloxamer 188.

The mixture of Candesartan Cilexetil, PVP K-30 and Poloxamer 188 was wetted with 50% ethanol was added and kneaded thoroughly for 30 min in mortar. The homogeneous paste was air dried for 24h and dried Slurry was air dried for 24 hours, Pulverized, pass through sieve no. 60 and evaluated for solubility.

Table 4: Ternary Solid dispersion of drug with PVP K-30 and Poloxamer 188

Sr. No.	Carrier	Ratio
1	PVP K-30 + Poloxamer 188	1:2:0.5
		1:2:1
		1:2:1.5
		1:2:2

Optimization of Superdisintegrants in Tablet Formulations

Preparation of sublingual tablets by direct compression method

Sublingual tablets of Candesartan Cilexetil were prepared by direct compression. All the ingredients were passed through # 80-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg by direct compression method using 8 mm flat punches on a Double Rotary Tablet Compression Machine (Rimek 10 station minipress). For optimization of superdisintegrant different types of disintegrants were selected like Crospovidone, Cross carmellouse sodium, Sodium starch glycolate at same concentration (3%). Tablets were prepared by direct compression.

Table 5: Composition of batches F1 to F6

Batches	F1	F2	F3	F4	F5	F6
Ingradients	Quantity per tablet (mg)					
Drug +β-cd complex	19.2	19.2	19.2	19.2	19.2	19.2
Crospovidone	3.6	-	-	3.6	-	-
Cross carmellouse sodium	-	3.6	-	-	3.6	-
Sodium starch glycolate	-	-	3.6	-	-	3.6
Mannitol	36	36	36	36	36	36
MCC	56.4	56.4	56.4	45.12	45.12	45.12
Lactose	-	-	-	11.28	11.28	11.28

Aspartame	1.2	1.2	1.2	1.2	1.2	1.2
Talc	2.4	2.4	2.4	2.4	2.4	2.4
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2
Total	120	120	120	120	120	120

Powder Characteristics of batches F1 to F6

Bulk density:

Weigh accurately 5 g powder (M), which was previously passed through 60 # sieve and transferred in 50 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula

Bulk density = Weight of powder / Bulk volume ..... (1)

Tapped density

Weigh accurately 5 g Powder, which was previously passed through 60 # sieve and transfer in 50 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2). Calculate the tapped bulk density in gm/ml by the following formula:

Tapped Density = Weight of powder / Tapped volume ..... (2)

Carr's index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD ..... (3)

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner's Ratio = TD / BD ..... (4)

Angle of repose

The angle of repose of powder mixture was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Where, h and r are the height and radius of the powder cone respectively.

$\tan \theta = h/r$ .....(5)

Evaluation of Batches F1 to F6

Hardness

The hardness of the tablets was determined by Pfizer hardness tester. A tablet hardness of about 3-4 kg is considered adequate for mechanical stability. Determinations were made in triplicate.

Thickness

The thicknesses of sublingual tablets were determined using micrometer screw gauge. Three individual tablets from each batch were used and the average thickness was calculated.

Weight Variation

It was performed as per the method given in the united state pharmacopoeia. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

%Friability

The tablets were tested for friability testing using Roche friabilator. For this test, ten tablets were weighed and subjected to combined effect of abrasion and shock in the plastic chamber of friabilator revolving at 25 rpm for 4 min, and the tablets were then dusted and reweighed.

***In-vitro* disintegration test**

In the USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual dosage form. The test was carried out using tablet disintegration apparatus (Model ED-2L, Electrolab, Mumbai, India). *In vitro* disintegration test was carried out using a modified disintegration method (n=6) using disintegration tester at 37± 0.5°C in distilled water. The tablets were kept in the basket and noted the time taken for the tablet to disintegrate completely into smaller particles.

Wetting time

The tablet was placed at the center of 2 layers of absorbent paper fitted into a petri dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

Drug content

Tablets (n=5) were weighed accurately and finely powdered. A quantity equivalent to 4 mg Candesartan Cilexetil was transferred to a 100 ml Volumetric flask. The drug was extracted in phosphate buffer pH 6.8 and the solution was filter by whatman filter paper. The absorbance was measured at 255 nm after suitable dilution using a Shimadzu UV-1800 (UV/Visible is double beam spectrophotometer).

***In-vitro* drug release study**

Dissolution study was conducted for all the formulations using USP dissolution rate test apparatus type-II (TDT-08L Electrolab, Mumbai, India.). Three hundred milliliters of phosphate buffer pH 6.8 was taken in dissolution apparatus which was maintain at 37ºC ± 0.5ºC at 100 rpm. Five milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 2 minute intervals and filtered by whatman filter paper. Samples were analyzed spectrophotometrically at 255 nm.

Optimization of Concentration of Superdisintegrant in Tablet Formulations

Table 6: Composition of Batches F7 to F9

Formula	F7	F8	F9
Ingradients	Quantity per tablet (mg)		
Drug +β-cd complex	19.2	19.2	19.2
Crospovidone (3%)	3.6	-	-
Crospovidone (4%)	-	4.8	-
Crospovidone (5%)	-	-	6.0
Mannitol	36	36	36
MCC	56.4	55.2	54.0
Aspartame	1.2	1.2	1.2
Talc	2.4	2.4	2.4
Aerosil	1.2	1.2	1.2
Total	120	120	120

Powder Characteristics of batches F7 to F9

Powder characteristics of batches F7 to F9 evaluated as per discussed in earlier section

Preparation of sublingual tablets by direct compression method

Sublingual tablets of Candesartan Cilexetil were prepared by direct compression discussed in section.

Evaluation of Batches F7 to F9

Batches F7 to F9 were evaluated for Hardness, Wetting time, *In-vitro* disintegration test, % Assay, % Friability, Uniformity of weight , *In-vitro* drug release study.

***Ex-Vivo* Permeation Study of Optimized Sublingual Tablet**

Buccal mucosa is very similar to the sublingual mucosa so in this study Goat buccal mucosa is used to check the permeation of drug thru the mucosa using Franz diffusion cell at 37 ± 0.5^{0}C.

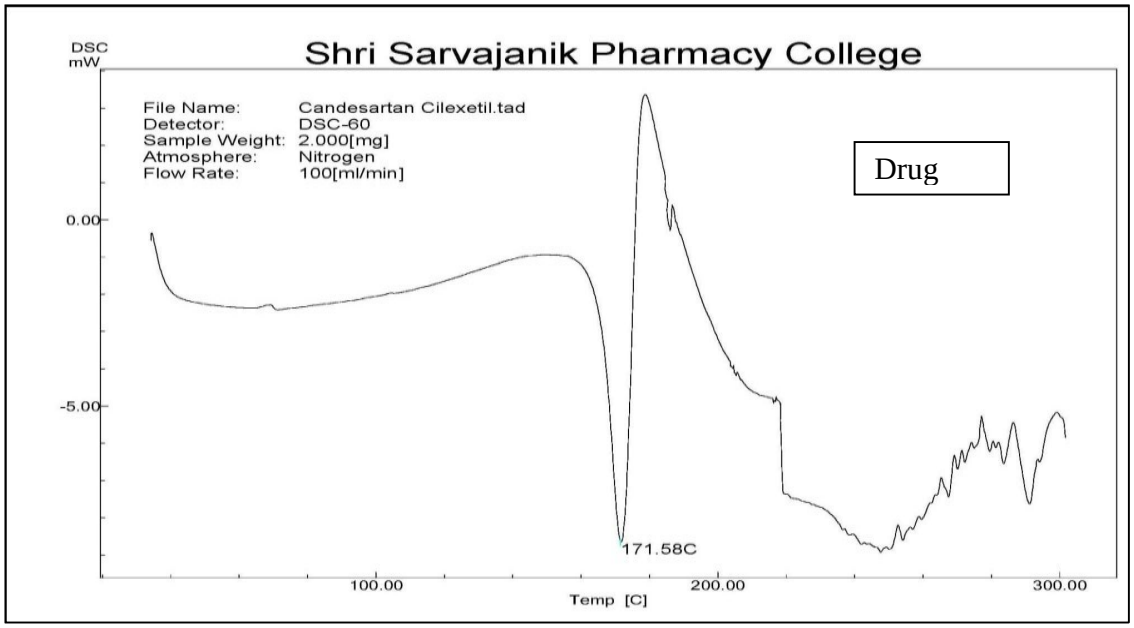
Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The sublingual tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 2 ml of phosphate buffer pH 6.8. The receptor compartment (72 ml capacity) was filled with phosphate buffer pH 6.8 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. Five milliliter samples were withdrawn at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 255 nm.

Stability Studies of the Optimized Formulation

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines Q1C. The stability studies were carried out on the optimized formulations as per ICH guidelines Q1C. The optimized formulation sealed in aluminum packaging and kept in humidity chamber maintained 40 ± 2 °C / 75 ± 5 %RH for 1 month. The optimized formulation sealed in aluminium foil was also kept at room temperature and humidity condition. At the end of studies, samples were analyzed for the hardness, wetting time, disintegrating time, *In-vitro* drug release and % drug content.

RESULTS AND DISCUSSION

Differential Scanning Calorimeter (DSC) study



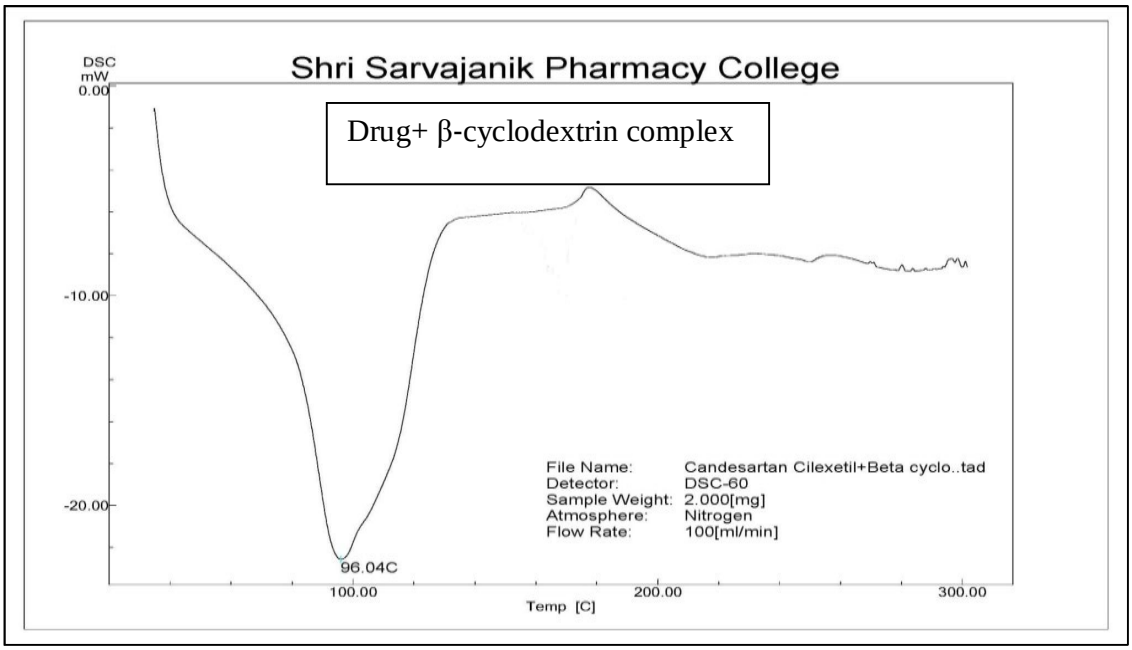
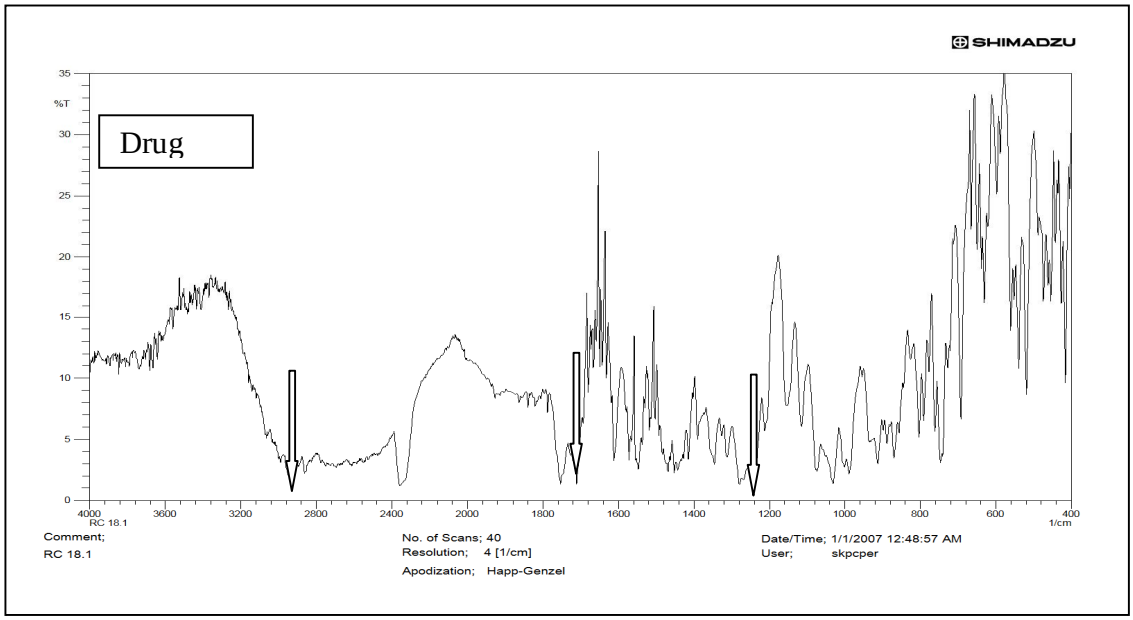


Figure 6: DSC spectrum

FT-IR Spectrophotometric Study for Compatibility



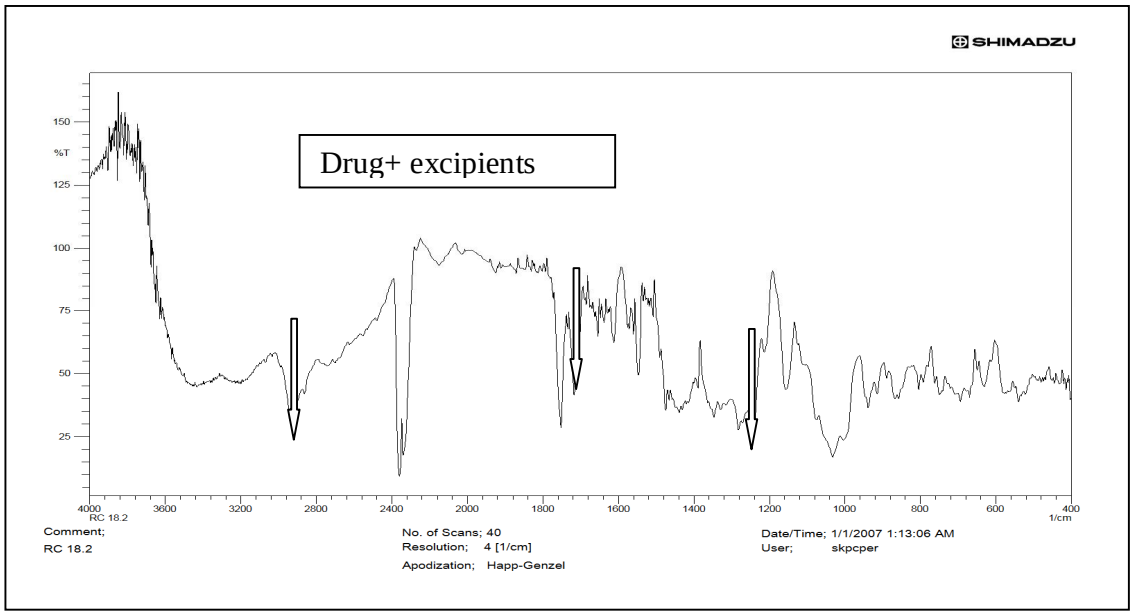


Figure 4: FTIR spectrum of drug + excipients

Fourier transform infrared (FT-IR) spectra of Candesartan Cilexetil, and a mixture of Candesartan Cilexetil with major excipients recorded over a range of 400-4000 cm^{-1} using KBr mixing method on FT-IR instrument (FT-IR 8400S, Shimadzu, Kyoto, Japan).

Table 7: Characteristic peaks of Candesartan Cilexetil and excipients in FTIR spectrum

Functional group	Range (cm^{-1})	Inferences (cm^{-1})
C-H	3000 - 3100	3080
C=O	1670 - 1820	1720
C-N	1080 - 1360	1250

The FT-IR of Candesartan Cilexetil showed C-H aromatic stretching, C=O Streching and C-N stretching values were meet their reported values.

The frequencies of functional groups of the drug Candesartan Cilexetil remained intact in physical mixture containing different excipients. So, it was concluded that there was no major interaction occurred between the drug and excipients used in the study.

Phase Solubility Study

Table 8: Solubility results of physical mixture of drug with different carriers

Solubility of drug in phosphate buffer pH 6.8= 15.757 mcg/ml				
Sr. No.	**Carriers**	**Ratio**	**Absorbance**	**Solubility (mcg/ml)**
1	Drug	1	0.014	15.757
2	PEG 4000	1:1	0.023	21.212
3	PEG 6000	1:1	0.03	25.455
4	PVP K-30	1:1	0.043	33.333
5	Poloxamer 188	1:1	0.024	21.818
6	Poloxamer 407	1:1	0.021	19.394
7	PVA	1:1	0.02	16.364
8	β-cyclodextrin	1:0.5 (Molar ratio)	0.041	32.121

From the Solubility results of drug with different carriers it was found that drug showed maximum solubility in PVP K-30 and β-cyclodextrin. So, both carriers were used for further studies.

Table 9: Solubility results of physical mixture of drug with PVP K-30 and β-cyclodextrin

Sr. No.	Carrier	Ratio	Absorbance	Solubility (mcg/ml)
1	PVP K-30	1:1	0.045	34.545
		1:2	0.048	36.364
		1:3	0.047	35.758
		1:4	0.045	34.545
2.	β-cyclodextrin	1:0.5	0.042	32.727
	(Molar ratio)	1:1	0.071	50.303
		1:1.5	0.117	78.182
		1:2	0.125	83.030

From the solubility results of physical mixture of drug with PVP K-30 and β-cyclodextrin in Different ratio. It was found that drug showed maximum solubility in 1:2 molar ratio of β-cyclodextrin.

Table 10: Solubility results of solid dispersion of drug with PVP K-30 and β-cyclodextrin

Sr. No.	Carrier	Ratio	Absorbance	Solubility (mcg/ml)
1	PVP K-30	1:1	0.056	41.212
		1:2	0.247	156.969
		1:3	0.234	149.091
		1:4	0.209	133.939
2.	β-cyclodextrin	1:0.5	0.124	82.424
	(Molar ratio)	1:1	0.265	167.878
		1:1.5	0.352	220.606
		1:2	0.437	272.121

From the solubility results of solid dispersion of drug with PVP K-30 and β-cyclodextrin in different ratio. Drug + β-cyclodextrin complex (1:2 Molar ratio) showed maximum Solubility.

Table 11: Ternary solid dispersion of drug with PVP K-30 and Poloxamer 188

Sr. No.	Carrier	Ratio	Absorbance	Solubility (mcg/ml)
1	PVP K-30 + Poloxamer 188	1:2:0.5	0.137	90.303
		1:2:1	0.264	167.273
		1:2:1.5	0.217	137.576
		1:2:2	0.193	124.242

From the solubility results Drug+β-cyclodextrin complex in molar ratio (1:2) showed maximum solubility. So, Drug+β-cyclodextrin complex (1:2) is used for tablet formulation.

Optimization of Superdisintegrant in Tablet Formulations

Table 12: Results of powder characteristics for batch F1 to F6

Batches	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
F1	24.56	0.417	0.476	12.50	1.143
F2	22.90	0.455	0.588	22.73	1.294
F3	23.59	0.435	0.568	23.48	1.307
F4	26.98	0.526	0.667	21.05	1.267
F5	27.84	0.556	0.714	22.22	1.286
F6	24.14	0.543	0.714	23.91	1.314

All the Powder mixture showed minimum carr's index, hausner's ratio and angle of repose. So, all the mixture had good flow properties. So we had gone through direct compression.

Table 13: Results of evaluation of batches F1 to F6

Batches	Hardness (n=3)	Thickness (n=3)	Weight variation (n=20)	Friability
F1	3.53±0.12	2.07±0.02	120.9±1.37	0.21
F2	3.57±0.21	2.04±0.01	121.2±1.46	0.33
F3	3.83±0.32	2.08±0.02	120.2±1.42	0.24
F4	2.60±0.17	2.13±0.01	121.1±1.50	0.30
F5	2.93±0.23	2.12±0.03	120.8±1.35	0.48
F6	2.73±0.31	2.14±0.02	121.5±1.59	0.37

Batches	Disintegration time	Wetting time	Drug content
F1	21.83±0.75	42.67±2.31	99.50±0.35
F2	30.17±1.47	57.00±2.65	98.38±0.17

F3	41.33±1.75	78.33±3.06	100.91±0.80
F4	27.50±1.64	53.67±2.52	99.90±0.70
F5	36.00±1.41	65.33±3.21	100.81±0.97
F6	48.17±1.83	72.67±1.53	101.31±0.18

All values are mean ± S.D

Batches F1, F2 and F3 showed Crospovidone, Croscarmellose sodium and Sodium starch glycolate in concentration of 3% and Microcrystalline cellulose alone in F1 to F3 batches.

Batches F4, F5 and F6 showed Crospovidone, Croscarmellose sodium and Sodium starch glycolate in concentration of 3% and containing 20% lactose of the total Microcrystalline cellulose.

The optimization of superdisintegrant was done based on the evaluation parameters like hardness, disintegration time, wetting time, % friability and % assay.

In the preliminary trial for optimization of superdisintegrant, all the prepared batches were evaluated firstly for the hardness. All the batches had hardness between 2.60 to 3.83 (kg/cm^2).

Disintegration time (sec) of batch F1 (3.6 mg) and batch F4 (3.6 mg) which were prepared with Crospovidone shown minimum disintegration time among all tablet formulation.

Batch F1 shows minimum wetting time 42.67±2.31 sec among all tablet formulation and minimum friability 0.21. So, superdisintegrant Crospovidone was optimized.

Table 14: *In-vitro* Drug release profile of batches F1 to F6

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	38.18±0.46	33.11±0.47	29.09±0.60	35.38±0.69	31.21±0.80	27.80±0.35
4	49.73±1.05	41.31±0.35	36.7±1.15	45.67±0.83	36.81±0.53	31.30±0.37
6	60.62±0.55	48.43±0.80	45.56±0.29	54.38±0.59	42.03±0.70	38.93±0.40
8	68.2±0.69	54.06±1.21	51.53±0.99	65.92±0.49	52.56±0.49	50.02±0.69

10	74.37±0.81	61.14±1.16	55.23±0.35	70.61±1.02	60.83±1.07	54.92±0.84
15	80.12±1.03	66.13±0.85	58.08±0.61	78.23±0.88	64.61±0.55	59.58±0.76
20	86.3±0.98	71.26±0.50	64.37±1.12	82.53±0.93	70.47±1.05	64.08±0.95
25	90.06±0.59	80.02±1.44	68.32±0.13	85.93±0.85	76.34±0.84	69.24±0.71
30	94.47±0.40	85.26±1.45	73.69±0.70	90.93±0.31	84.34±0.79	76.98±0.51

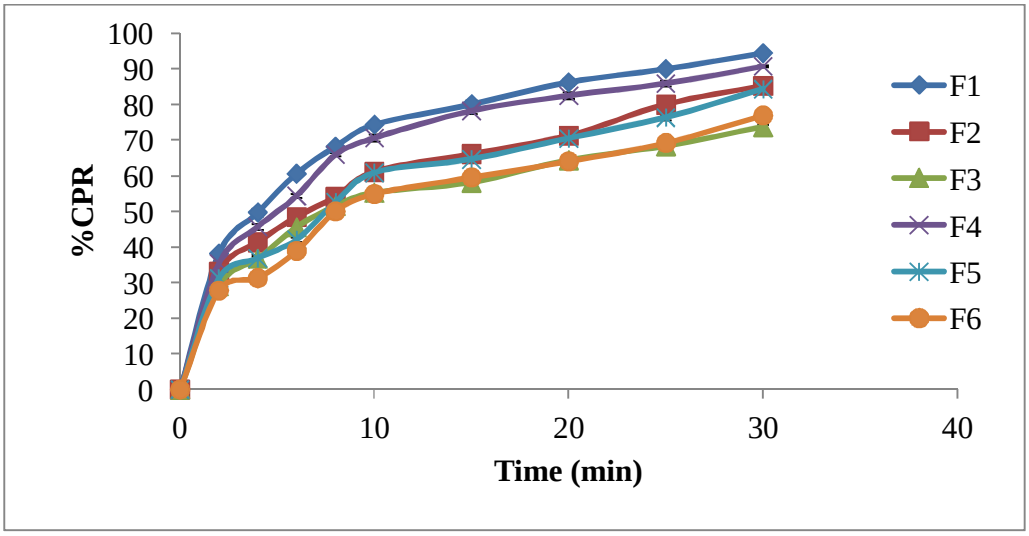


Figure 11: *In-vitro* Drug release profile of batches F1 to F6

Here there was no any significant effect of lactose on *In vitro* drug release and also tablet containing lactose having high friability and less hardness. The highest amount of drug release was done in F1 batch containing 3% CP and microcrystalline cellulose alone. So optimization of concentration of CP carried out with MCC alone as diluent.

Optimization of Concentration of Superdisintegrant in Tablet Formulations

Table 15: Results of powder characteristics for Batch F7 to F9

Batches	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
F7	24.50	0.417	0.476	12.50	1.143
F8	22.62	0.435	0.526	17.39	1.211

F9	23.88	0.424	0.500	15.25	1.180

All the Powder mixture showed minimum carr's index, hausner's ratio and angle of repose. So all the mixture had good flow properties. So we had gone through direct compression.

Table 16: Results of Evaluation of batches F7 to F9

Batches	Hardness (n=3)	Thickness (n=3)	Weight variation (n=20)	Friability
F7	3.67±0.12	2.07±0.01	121.3±1.36	0.20
F8	4.030±.15	2.09±0.02	121.4±1.30	0.22
F9	3.930. ±23	2.12±0.02	121.1±1.22	0.19

Batches	Disintegration time	Wetting time	Drug content
F7	21.50±1.10	38.00±2.65	99.70±0.61
F8	17.33±1.05	30.67±1.53	99.59±0.63
F9	11.83±1.17	28.33±3.06	100.52±0.46

All values are mean ± S.D

Batches F7, F8 and F9 showed Crospovidone in concentration range of 3%, 4% and 5% respectively.

The optimization of concentration of Crospovidone as superdisintegrant was done based on the evaluation parameters like hardness, disintegration time, wetting time, % friability and % assay.

All the prepared batches were evaluated firstly for the hardness. All the batches had hardness between 3.67 to 4.03 (kg/cm^2).

Disintegration Time (sec) time of Batch F9 which was prepared with Crospovidone (5%) shown minimum disintegration time among all tablet formulation.

Batch F1 shows minimum wetting time 28.33±3.06 sec among all tablet formulation and minimum friability 0.19. So, Batch F9 containing 5% CP was optimized.

Table 17: *In-vitro* drug release profile of batches F7 to F9

Time (min)	F7	F8	F9
0	0	0	0
2	37.18±0.60	42.12±0.35	49.01±0.26
4	48.77±0.68	52.6±0.70	60.44±0.92
6	59.61±0.57	61.64±0.93	71.58±0.41
8	67.23±0.49	70.98±0.69	80.55±1.38
10	74.58±0.82	78.63±0.72	85.25±0.96
15	81.15±0.50	84.58±0.77	91.98±1.30
20	87.3±0.94	89.54±0.63	94.71±0.29
25	90.21±0.73	93.88±0.51	98.06±0.28
30	93.76±0.31	96.23±0.54	100.10±0.17

Batches F7, F8 and F9 showed Crospovidone in concentration range of 3%, 4% and 5% respectively.

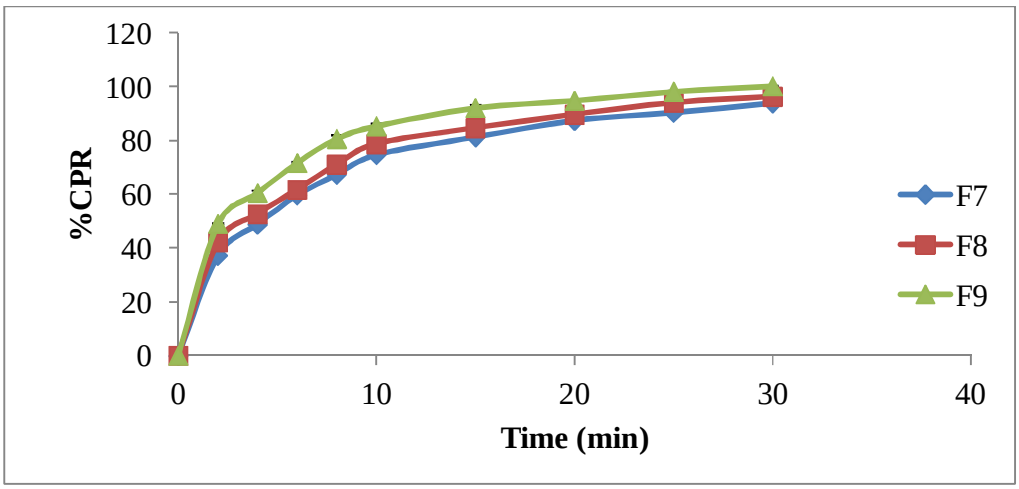


Figure 5.12: *In-vitro* Drug release profile of batches F7 to F9

Batches F7, F8 and F9 showed Crospovidone in concentration range of 3%, 4% and 5% respectively. 100% drug release was done within 30 minute for the batch F9 containing 5% CP. More than 90% drug release was done within 15 min.

Ex-vivo permeation study of optimized batch

Table 18: _Ex-vivo_ permeation study of optimized batch

Time (min)	% CPP
0	0
2	8.455
4	14.11
6	21.58
8	30.06
10	38.49
15	47.68
20	59.83
25	73.36
30	87.23

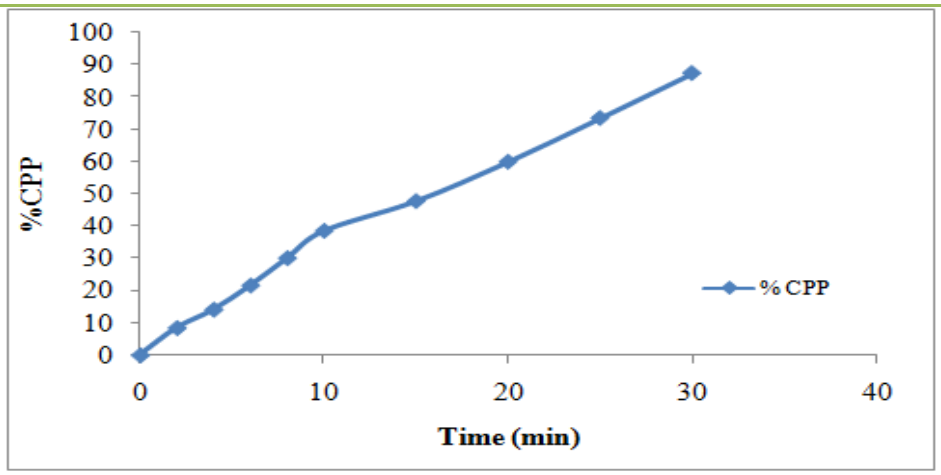


Figure 5.14: Plot of _Ex-vivo_ permeation of optimized batch

Ex-vivo permeation study was conducted for 30 min and at 30 min permeation of optimized batch F9 was found 87.23%.

Short Term Stability Study of Optimized Formulation

Table 19: Storage condition

Batch	Storage condition
A	Room temperature and humidity condition
B	40 ± 2°C / 75 ± 5 %RH

Table 20: Evaluation after stability

Parameters	Initial Batch	Batch A	Batch B
Hardness	3.93±0.23	3.87±0.35	3.53±0.12
Disintegration time	11.83±1.17	11.57±1.03	10.65±1.41
Wetting time	28.33±3.06	27.45±1.17	25.93±2.07
Drug content	100.52	99.90	99.48

Table 21: Comparison of dissolution profile after stability study

Time (min)	Initial batch F9	After 25^0C	After 40^0C
0	0	0	0
2	49.01±0.26	48.49±0.47	47.35±0.95
4	60.44±0.92	59.67±0.91	58.67±0.15
6	71.58±0.41	70.28±0.82	68.95±0.71
8	80.55±1.38	80.43±0.53	79.54±0.35
10	85.25±0.96	85.44±1.02	83.92±0.43
15	91.98±1.30	92.47±0.67	90.40±1.48
20	94.71±0.29	95.28±0.33	92.88±1.21

25	98.06±0.28	97.43±0.16	96.51±0.56
30	100.10±0.17	99.37±0.73	98.89±0.23

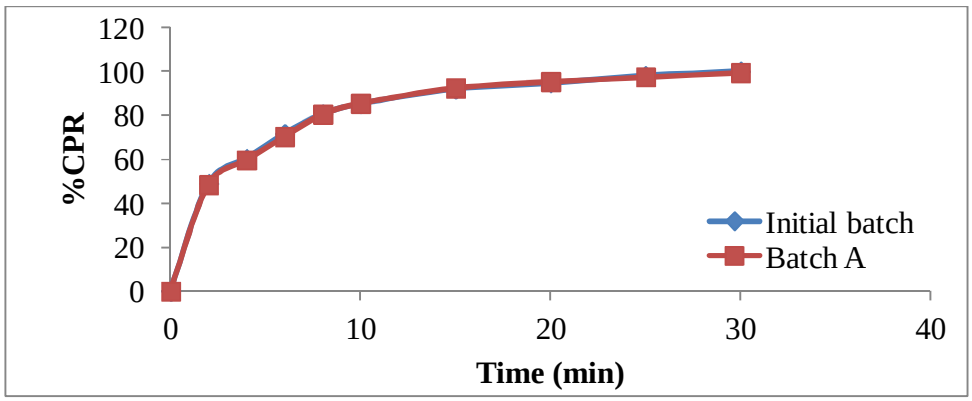


Figure 15: Comparison of dissolution profile between Initial batch and batch A after stability study

Before stability study drug content was found 100.52% for Initial batch (F9). After stability study drug content was found 99.90% for batch A and similarity value (f2) was found to be 90.648 which indicates no sigficant difference in dissolution profile. Hence, we can conclude that formulation was stable.

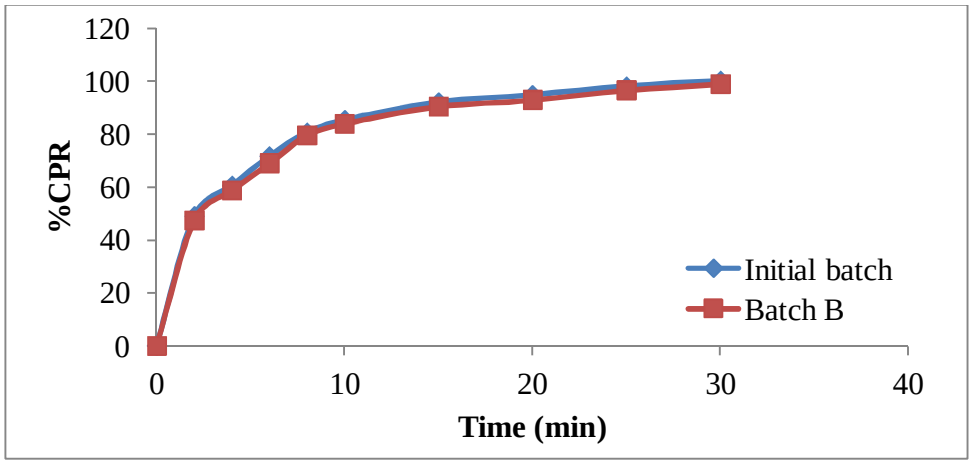


Figure 16: Comparison of dissolution profile between Initial batch and batch B after stability study

Before stability study drug content was found 100.52% for Initial batch (F9). After stability study drug content was found 99.48% for batch B and similarity value (f2) was 75.630 which indicates

no significant difference in dissolution profile. Hence, we can conclude that formulation was stable.

Comparision of the Optimized Formulation with Marketed Formulation

Table 22: *In-vitro* drug release profile of optimized batch and marketed product

Time (min)	Optimized batch (F9)	Marketed product
0	0	0
2	49.01±0.26	7.73±0.23
4	60.44±0.92	12.25±0.80
6	71.58±0.41	18.21±0.75
8	80.55±1.38	25.10±0.39
10	85.25±0.96	30.43±0.92
15	91.98±1.30	37.28±0.84
20	94.71±0.29	43.49±0.77
25	98.06±0.28	50.69±0.53
30	100.10±0.17	58.31±0.62

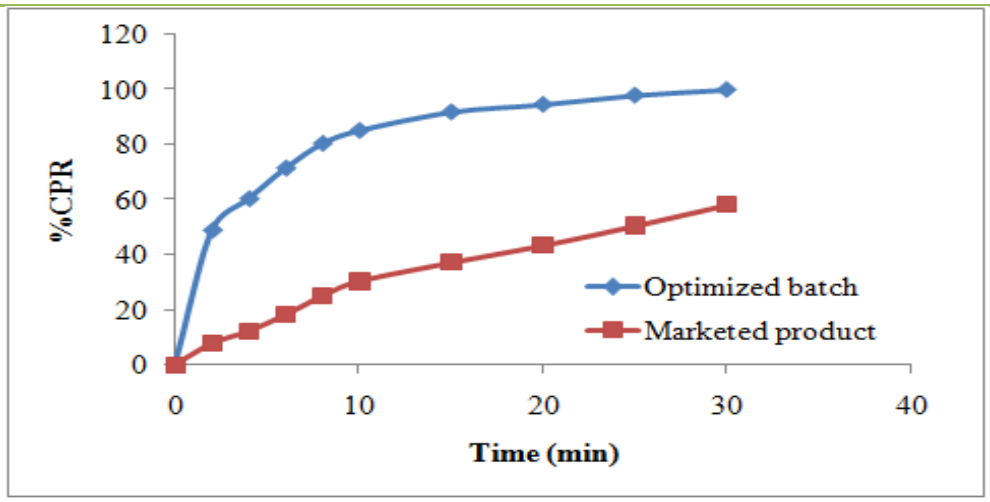


Figure 17:Comparision of *In-vitro* Drug release between optimized batch and marketed product

Comparision of the optimized formulation with marketed formulation result showed that only 58.31±0.62% drug release within 30 min was done from marketed product.

CONCLUSION:

From this study, it was concluded that Candesartan Cilexetil sublingual tablet were prepared successfully by the use of Candesartan Cilexetil + β-cyclodextrin complex in Molar ratio 1:2 using Crospovidone as superdisintegrant. It was concluded that Candesartan Cilexetil + β-cyclodextrin complex in molar ratio 1:2 was successfully improved the solubility of Candesartan Cilexetil. Sublingual delivery of Candesartan Cilexetil may also provide fast onset of action and improve patient compliance. The optimized formulation was found stable.

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