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FORMULATION DEVELOPMENT AND EVALUATION OF ORAL DISINTEGRATING TABLET OF CANDESARTAN CILEXETIL.

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ABSTRACT

Candesartan cilexetil is selective AT1 subtype angiotensin II receptor and it is used in treatment of hypertension, heart failure and myocardial infarction. The oral disintegrating tablets as recently developed drug delivery system. Candesartan cilexetil should be administrated orally once or twice daily for a total daily dose of 4 to 32 mg. In this investigation oral disintegrating tablet were prepared by using super disintegrating agent crospovidone, croscaremellose sodium, sodium starch glycolate in concentration 3%, 4%, 5%. Sweeteners and flavors were used to enhance the organoleptic properties of tablet. Tablets were prepared by direct compression technique. Formulated oral disintegrating tablets were evaluated for weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release. The results show that the all formulations satisfied the limits of oral disintegrating tablet. The formula [F9] that contain 5% crospovidone as superdisintegrant shows the best results with a disintegrating time 31 sec, hardness 3.7 kg/cm^2 and drug release rate 98.08% within 10 min.

KEYWORDS: Candesartan cilexetil, oral disintegrating tablet, crospovidone.

INTRODUCTION

Recent market studies indicate that more than half of the patient population prefers oral disintegrating tablets to other dosage forms and most consumers would ask their doctors to prescribe oral disintegrating tablets (70%), purchase oral disintegrating tablets (70%), or prefer oral disintegrating tablets to regular tablets or liquids (>80%).[1]

The pediatric and geriatric patients are of particular concern. To overcome this dispersible tablets and fast-disintegrating tablets have been developed. Most commonly used methods to prepare these tablets are freeze-drying/lyophillization, tablet molding and direct compression methods. Main advantages of direct compression method are low manufacturing cost and high mechanical integrity of the tablets. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion). The dissolution of drug can also be influenced by disintegration time of the tablet. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.[2]

Candesartan Cilexetil is an ester prodrug. Candesartan Cilexetil is chemically 2-ethoxy-3-[21-(1*H*-tetrazol-5-yl) biphenyl-4 methyl]-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.[3, 4]

Hence, in the present research work fast dissolving tablets of Effect of Candesartan cilexetil will be prepared by using different super disintegrates. Effect of various super disintegrants on dissolution rate, disintegration time and wetting time will be studied.

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 bio activated 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. Diet with a high fat content has no affect on the bioavailability of Candesartan from Candesartan Cilexetil.[7]

MATERIAL AND METHODS

Material

Candesartan cilexetil was received as gift sample from Ranbaxy Laboratories Ltd. Dewas M.P. (India). Croscarmellose sodium, crospovidone, sodium starch glycolate, and aspartame were received as gift from Cris Pharma. India Ltd. Dehradun.and mannitol, microcrystalline cellulose, vanilla flavor and Mg stearate were procured from SD Fine Chemicals, Mumbai.

Methods

Preparation of standard curve of Candesartan cilexetil

The samples of different concentration were analyzed at 277 nm using UV-Spectrophotometer against 6.8 pH phosphate buffer as blank.

Drug excipient compatibility studies

Drug excipient interaction were studied using FTIR spectroscopy. The spectra were recorded for pure Candesartan cilexetil and with excipient mixture. The spectra were recorded for Candesartan cilexetil physical mixture of excipient and physical mixture of drug with excipient using FTIR-spectrophotometer from KBr pellets. The scanning range was 400-4000cm^{-1}.

Formulation development

Candesartan cilexetil oral disintegrating tablets were prepared by direct compression method according to the formula as described in table 2. The drug was mixed with proper portion of superdisintegrants. Care should be taken to confirm the proper mixing of drug and superdisintegrants. Then other excipients were added. Then the mixture is passed through sieve No. 44. The mixture is blended with, lubricating agent (magnesium stearate) and filler. Finally the blend is subjected for compression using 10mm on Clit pilot press 10 Station machine.

Table: 1

Ingredients	Formulations								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Candesartan cilexetil	16	16	16	16	16	16	16	16	16
Microcrystalline cellulose	310	306	302	310	306	302	310	306	302
Mannitol	50	50	50	50	50	50	50	50	50
Croscarmellose sodium	12	16	20	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	12	16	20			
Crospovidone	-	-	-				12	16	20
Aspartame	5	5	5	5	5	5	5	5	5
Vanilla flavor	2	2	2	2	2	2	2	2	2
Mg stearate	5	5	5	5	5	5	5	5	5
Total tablet weight (mg)	400	400	400	400	400	400	400	400	400

Characterization of blend[8]

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was calculated using the following formula:

$\tan \theta = h/r$

Therefore $\theta = \tan^{-1} (h/r)$

Where, θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Bulk density

A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. Bd was calculated using the following equation;

Bulk Density (Bd)**:** Mass/Bulk volume.

Tapped density

A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. Tapped density was calculated using the following equation

Tapped Density (Td)**:** Mass/Tapped volume

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's ratio = Tapped density/ Bulk density.

Compressibility index (Carr's Index)

Weighed quantity of powder was taken in a graduated cylinder upto 70ml marking and was tapped in density tester for 500taps/ 750 taps/ 1250 taps, till the level of powder in measuring cylinder remains same after tapping. The final volume was then observed and Bulk density, Tapped density and compressibility index.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped Density}} \times 100$$

Evaluation of prepared tablets[9]

Hardness of tablets

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Several devices used to test tablet Hardness, the Monsanto tester, the Strong-Cobb tester, the Pfizer tester and the Schleuniger tester. It is expressed in kg/cm^2.A hardness 4 kg/cm^2 is considered minimum for a satisfactory tablet. Six tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Friability tablet

Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula:

$\%F = \{(W_0 - W)/W_0\} \times 100$

Where, %F= Friability in percent

W_0 = Initial weight of tablet

W = weight of tablet after test.

Weight variation test

The USP weigh variation test was performed by weighting 20 tablets individually, calculating the average weigh and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Drug content[10]

Ten tablets were weighed and powdered and 50 mg equivalent weight of Candesartan cilexetil was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with 6.8 pH Phosphate buffer. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 277 nm using UV-Visible spectrophotometer (Shimadzu UV-1800). The drug content of each sample was estimated from standard curve of Candesartan cilexetil using 6.8 pH phosphate buffer.

Wetting time

The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (i.d. = 6.5 cm) containing 10 ml of pH 6.8 buffer, a tablet was put on the paper, and the time for complete wetting was measured. Three trials from each batch were performed and standard deviation was also determined.

Water absorption ratio

The water absorption ratios of the tablet were carried out in Petri dishes with p^H 6.8 phosphate buffer. Periodically, the tablets were withdrawn from the Petri dishes and weighed on electronic balance after removal of surface water by light blotting with a lab tissue for change of their weight till a constant weight is attained.

In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

One tablet in each of the 6 tubes of the basket is to be placed and the apparatus subjected to run. The assembly should be raised and lowered between 50 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. Disintegration or more specifically dispersion

times were measured in 900 ml pH 6.8 phosphate buffers without using disc at room temperature (37°C ±0.2°C).

In-vitro Dissolution Studies

In-vitro dissolution study was performed by using USP dissolution test apparatus (Apparatus II, Paddle type) at 50 rpm for 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min. in 6.8 pH phosphate buffer. 10 ml samples were withdrawn at the specified time intervals and replaced with 10ml of fresh dissolution medium, collected samples were filtered using whatman filter paper and analyzed. Calculate percentage drug release by UV Spectroscopy method.

RESULTS AND DISCUSSIONS

Preparation of calibration curve

Calibration curve of Candesartan cilexetil in 6.8 pH phosphate buffer (λ_{max} = 277 nm)

Table 2

S. N.	Concentration (µg/ml)	Absorbance
1	0	0
2	1	0.03
3	2	0.09
4	3	0.16
5	4	0.22
6	5	0.29
7	6	0.36
8	7	0.43
9	8	0.49
10	9	0.55
11	10	0.62

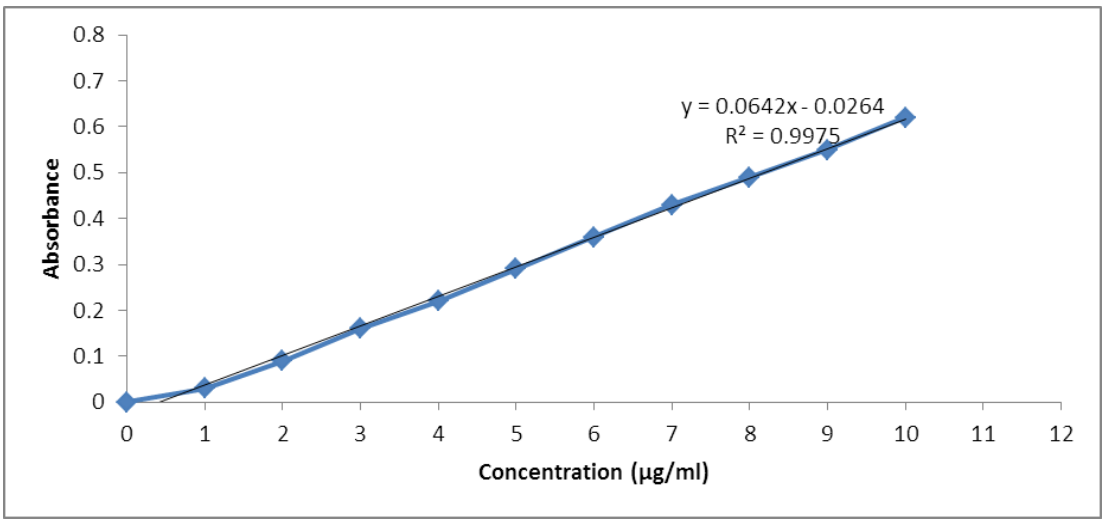

Fig. 1: Standard Calibration Curve of Candesartan cilexetil.

Compatibility study

Results of Drug-excipient compatibility studies by FTIR

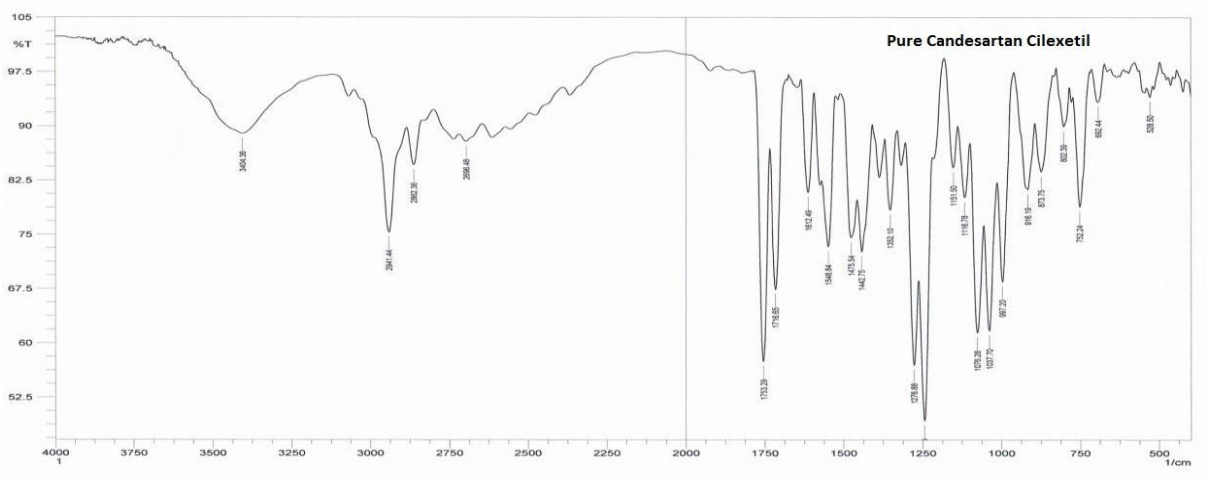

Fig. 2: IR spectrum of Candesartan cilexetil.

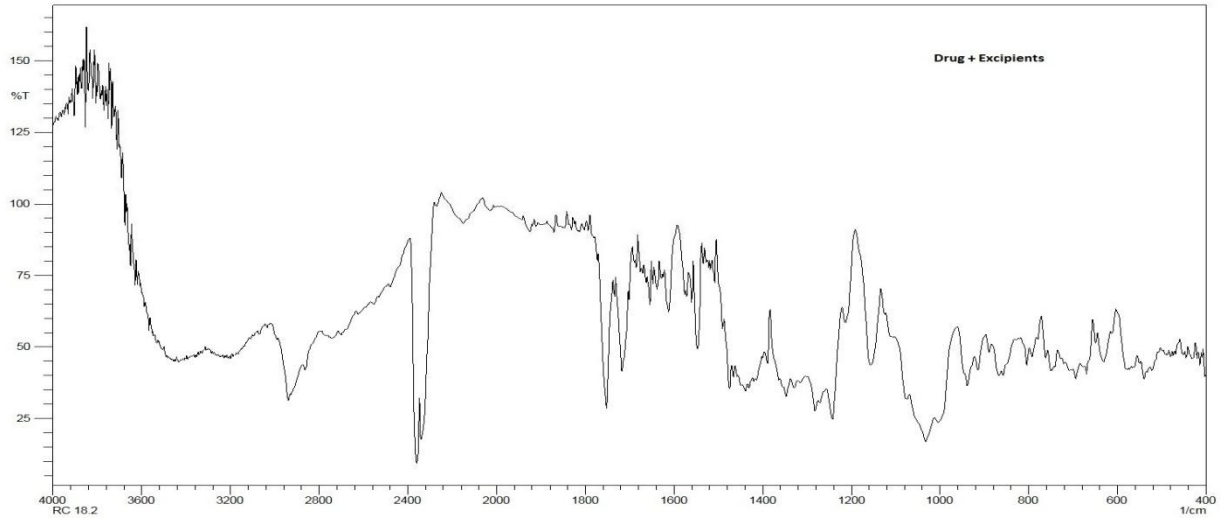

Fig. 3: IR spectrum of drug + Excipients.

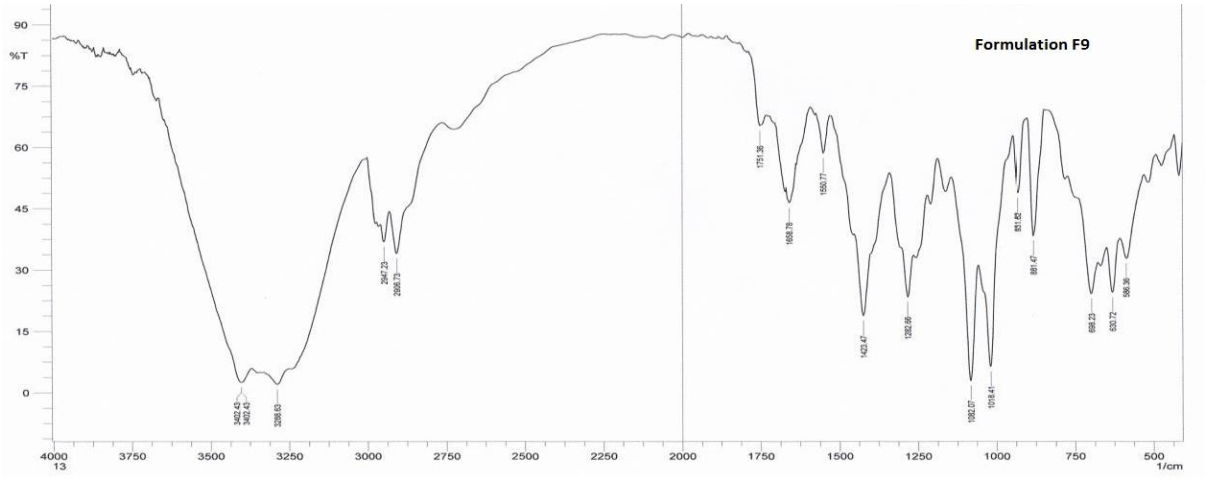

Fig. 4: IR spectrum of formulation F_9.

Characterization of blend

Angle of Repose (θ°)

The angle of repose for the formulated blend was carried out and the results were shown in table 3. It concludes all the formulations blend was found to be in the range 25°42' to 29°29'. Hence the entire formulations blend was found to be good flow property.

Compressibility index

Compressibility index was carried out, it found between 6.66% to 14.60% indicating the powder blend has the required flow property for compression table 3.

Hausner's ratio

Hausner's ratio was calculating for the blend, it found between 1.07 -1.17 indicating powder blend has the required flow property for compression table 3.

Loose bulk density

The loose bulk density for the formulated blend was carried out and the results were shown in table 3. It concludes all the formulations blend was found to be in the range 0.327- 0.4.

Tapped bulk density

Tapped bulk density was calculating for the blend, it found between 0.357 – 0.461 indicating powder blend has the required flow property for compression table 3.

Table 3

Formulation	Angle of repose (θ)	Loose bulk density (LBD)	Tapped bulk density (TBD)	Carr's index %	Hausner ratio
F_1	29.29	0.4	0.461	13.23	1.15
F_2	27.34	0.377	0.402	7.12	1.08
F_3	27.68	0.352	0.4	12	1.14
F_4	27.33	0.327	0.357	8.57	1.09
F_5	26.56	0.35	0.375	6.66	1.07
F_6	25.42	0.338	0.381	13.15	1.15
F_7	27.69	0.368	0.421	12.58	1.14
F_8	26.95	0.36	0.42	14.2	1.16
F_9	25.79	0.35	0.41	14.6	1.17

Evaluation of prepared tablets

Hardness test

The measured hardness of tablets of each batch ranged between 3.70-4.57 kg/cm^2. (table 4).this ensured good characteristics of all batches.

Friability

Friability of all formulations was within acceptable limits. The friability of the formulations of Candesartan cilexetil formulation $F_1$to F_9 respectively was found to be less than 1.0 %. The results were shown in table 4.

Weight variation test

The percentage weight variation for all the formulations were tabulated in table 4. All the formulations (F_1 to F_9) tablets passed weight variation test. The weights of all the batches were found to be uniform with low standard deviation values.

Water absorption ratio

Water absorption ratio ranged from 56.77-64.65 in formulation of Candesartan cilexetil. Crospovidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The results were shown in table 4.

Table 4

Formulation	Hardness (kg/cm2)	Thickness (mm)	Weight variation	Friability	Water absorption ratio
F_1	4.57±0.04	4	0.402±1.14	0.612±0.05	59.54±0.45
F_2	3.75±0.22	4	0.397±1.67	0.376±0.07	61.75±0.75
F_3	4.28±0.42	4	0.402±1.36	0.595±0.05	62.36±0.33
F_4	3.97±0.25	4	0.399±1.41	0.456±0.01	61.54±0.11
F_5	4.25±0.42	4	0.401±1.82	0.395±0.02	64.65±0.57
F_6	3.89±0.51	4	0.399±1.58	0.412±0.06	61.54±0.24
F_7	4.12±0.25	4	0.403±1.33	0.398±0.03	56.77±0.65
F_8	3.98±0.15	4	0.398±1.67	0.474±0.01	62.55±0.49
F_9	3.70±0.27	4	0.401±1.45	0.355±0.03	60.59±0.67

Wetting time

Wetting time is used as an indicator from the ease of the tablet disintegration in oral cavity. In formulation of Candesartan cilexetil (F_1 to F_9) observed that wetting time of tablets was in the range of 29.54 to 39.27 seconds. It was observed that type of the disintegrant affected the wetting of the tablets. The results were shown in table 5.

Drug content uniformity

The percentage of drug content for F_1 to F_9 was found to be 96.67% to 99.57% of Candesartan cilexetil. The results were shown in table 5.

Disintegration time

All the formulations complied with the dispersion time requirement of ≤180 sec for oral disintegrating tablets as per IP. Formulation F9 had the least dispersion time of 31 seconds. The results were shown in table 5.

Table 5

Formulation	Disintegrating time (Sec)	Drug content (%)	Wetting time (Sec)
F_1	36.54±0.57	98.65±0.58	33.54±0.07
F_2	38.65±0.58	98.65±0.29	35.11±0.22
F_3	33.96±0.56	97.52±0.45	32.76±0.45
F_4	34.64±0.54	98.76±0.43	34.86±0.17
F_5	37.27±0.25	99.01±0.81	36.75±0.03
F_6	38.45±0.55	98.08±0.57	38.77±0.15
F_7	36.95±0.56	96.67±0.74	29.54±0.54
F_8	35.45±0.54	98.83±0.41	39.27±0.43
F_9	31.00±0.67	99.57±0.52	30.58±0.55

In vitro dissolution studies

Dissolution Profiles of all formulations were compared by percentage of drug release versus time. From dissolution results it was confirmed that formulation F_9 was showing good dissolution profile.

Table 6

Time (min)	Formulations								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0	0	0	0	0	0	0	0	0	0
1	38.74	40.88	42.85	37.52	41.22	35.45	39.21	43.54	41.12
2	44.71	45.56	48.13	43.21	45.58	37.14	45.11	47.35	48.25
3	48.23	50.21	52.87	48.58	51.46	46.32	50.46	52.42	54.67
4	52.54	54.77	59.82	52.65	56.96	50.25	56.98	55.39	65.42
5	58.52	59.44	64.44	59.58	61.48	54.55	63.75	67.43	70.36
6	60.22	63.52	71.11	62.31	68.44	59.31	68.73	72.54	77.81
7	62.56	70.47	77.36	66.29	78.49	66.66	74.22	81.22	82.25
8	73.84	80.28	84.77	71.83	81.52	71.69	82.08	86.57	86.82
9	80.21	83.83	87.25	80.72	86.23	76.33	86.13	91.29	93.92
10	83.24	88.33	92.47	87.65	91.56	83.68	89.35	94.14	98.08

CONCLUSION

In the present work, an attempt was made to develop oral disintegrating tablets of Candesartan cilexetil From the study conducted, the following conclusions were drawn: Amongst the various combinations of superdisintegrants used in the study, tablets that were formulated (direct compression) using Crospovidone exhibited quicker disintegration of tablets than compared to those of sodium starch glycolate and Croscarmellose sodium.

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