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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF CANDESARTAN CILEXETIL IN BULK AND PHARMACEUTICAL DOSAGE FORMS BY THIRD ORDER DERIVATIVE SPECTROSCOPIC TECHNIQUE

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ABSTRACT: Candesartan cilexetil, a prodrug is a racemic mixture containing one chiral center at the cyclohexyloxy-carbonyloxy- ethyl ester group. It is soluble in dimethyl formamide, acetone, methanol, 0.1 N sodium hydroxide solution and insoluble in water. Objective of the present study is to develop a simple, sensitive, accurate, precise and rapid derivative spectrophotometric method for the estimation of candesartan in pure form. For the estimation of candesartan, solvent system employed was absolute methanol and wavelength of detection (λ_{det}) was 294.3 nm for third order derivative spectroscopy. The linearity was obtained in the range 180 – 280 $\mu\text{g/ml}$. The regression equation was found to be $y = 0.0001x + 0.003$ & regression coefficient, R^2 was found to be 0.999. The limit of detection is 6.7 $\mu\text{g/ml}$ and limit of quantification was found to be 20.4 $\mu\text{g/ml}$. Obtained results showed that there is minimum intraday and inter day variation. The developed method was validated and recovery studies were also carried out. Sample recovery using the above method was in good agreement with their respective labeled claims, thus suggesting the validity of the method and non-interference of formulation excipients in the estimation. Third order derivative spectroscopy method is simple, rapid and reproducible and further it can be used for the analysis.

INTRODUCTION: Candesartan cilexetil (prodrug is a racemic mixture containing one chiral center at the cyclohexyloxy-carbonyloxy- ethyl ester group. Angiotensin II receptor blockers (ARBs) are a new class of therapeutic agents for hypertension¹.

The ARBs have a more direct mechanism of action than other drugs affecting the angiotensin converting enzyme inhibitors¹.

Candesartan is a potent, highly selective ARB that is devoid of agonist activity. It is administered orally as Candesartan cilexetil, which is rapidly and completely hydrolyzed to Candesartan, the active moiety, during absorption from the gastrointestinal tract. Candesartan cilexetil is white to off white powder. It is soluble in dimethyl formamide, acetone, methanol, 0.1 N sodium hydroxide solution and insoluble in water¹.

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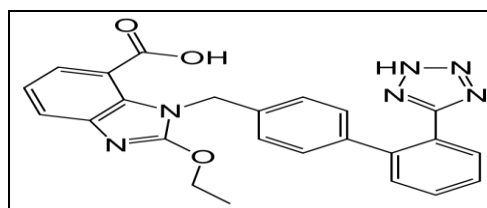


FIG. 1: STRUCTURE OF CANDESARTAN CILEXETIL

Literature review suggested several analytical methods that have been reported for the estimation of Candesartan in bulk or pharmaceutical formulations include High Performance Liquid Chromatography, and UV-Visible Spectrophotometry.

Literature review also suggested that there is no third order Derivative Spectroscopic method. The objective of the work was to develop simple, accurate, precise and economic third order derivative spectroscopic method to estimate the candesartan in bulk. The method should be simple, accurate, precise, reproducible and statistically valid.

MATERIALS AND METHODS:

Drug:

The standard sample of CANDESARTAN was obtained as gift sample from Dr. Reddy's Laboratory Pvt. Ltd., Hyderabad, A.P., India. The candesartan tablets were procured from local market, brand name CANDESAR (8mg), manufactured by RANBAXY Laboratories, India.

Instrument specifications:

UV Spectrophotometer, Shimadzu, model 1800.

Chemicals and reagents used:

Methanol obtained from local market, manufactured by Merck Pharmaceuticals.

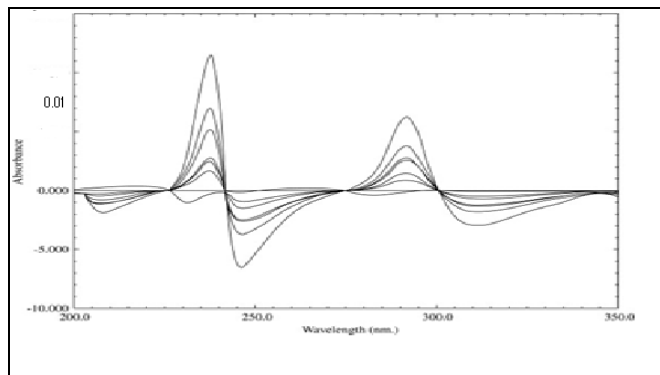
Preparation of stock solution:

The stock solution of candesartan is prepared by dissolving 100 mg of drug in 100 ml methanol in volumetric flask with continuous shaking. 1.8 ml of sample was withdrawn and diluted to 100 ml methanol to get 180 µg/ml of solution. The solution was then scanned in UV range between 200-400 nm UV-VIS Spectrophotometer, Shimadzu, Japan to determine the absorption maxima of the drug against blank as methanol.

Wavelength scanning and determination of absorption maximum:

From the stock solution of Candesartan, known concentration of 180µg/ml is prepared by suitable dilution with methanol. Wavelength scanned for the maximum absorption of drug solution using UV-Visible spectrophotometer within the

wavelength region of 200–400 nm against blank methanol. Convert the normal mode obtained spectra to second order derivative. The wavelength that shows the peak with a highest absorbance is considered as absorbance maximum of the drug. The result is presented in **Graph 1 & Table 1**.



GRAPH 1: DEPICTING LINEARITY & SELECTION OF ABSORBANCE MAXIMA.

Linearity studies for Candesartan analytical method:

Stock solution was subsequently diluted with methanol to get 180 µg/ml, 200µg/ml, 220µg/ml, 240µg/ml, 260µg/ml, 280µg/ml. Convert the normal mode obtained spectra to third order derivative. The results are tabulated and the linearity curve was constructed by plotting concentration Vs. D^3 value. The result is presented in **Table 1**.

Precision:

The precision of method was ascertained; the percent relative standard deviation were calculated and presented.

Inter day and intraday studies for Candesartan analytical method:

The prepared stock solution was subsequently diluted to get 220µg/ml. The resulting solution absorbance was measured at detection wavelength of 294.3 nm using double beam UV spectrophotometer against blank of methanol. The findings was made at different time intervals in day times in a day and performed continuously for six days. Convert the normal mode obtained spectra to third order derivative. The results obtained were tabulated and studied for inter day and intraday variation. The results are tabulated in **Table 2 and 3**.

Accuracy studies:

The accuracy/recovery studies were carried out by adding a known amount of drug from the pre-analyzed tablet powder and percentage recoveries were calculated. Convert the normal mode obtained spectra to third order derivative. The reproducibility of estimation was determined by performing the tablet drug content of different samples. The results of accuracy studies were expressed in %. The result is presented in **Table 4**.

Assay studies:

The assay studies were carried out with the help of candesartan marketed formulation (Candesar, 8 mg). The percentage purity was calculated. Convert the normal mode obtained spectra to third order derivative. The reproducibility of estimation was determined by performing the drug content of different samples. The results of assay studies were expressed in %. The result is presented in **Table 5**.

RESULTS AND DISCUSSION:

Candesartan Cilexetil is a novel, potent, highly selective non peptide angiotensin II type 1 (AT1)

receptor blocker which is administered orally as Candesartan cilexetil, which is rapidly and completely hydrolyzed to Candesartan, the active moiety, during absorption from the gastrointestinal tract. Different measured D^3 values at detection wavelength 294.3 nm is plotted as the curve as D^3 value vs. concentration. Candesartan obeys the beer's law in the concentration range 180 to 300 $\mu\text{g/ml}$. The linear regression equation is $y = 0.0001x + 0.003$ with correlation coefficient (R^2) = 0.999.

The developed method is validated for repeatability, reproducible and the accuracy and precision. In the inter day and intraday study of standard graph, the % RSD is less than 2% indicating the developed method is reproducible. The different levels of standard concentration solutions are measured for D^3 value and actual concentration is calculated. The results showed that the amount recovered is 100% indicating the third order derivative spectroscopic method is accurate and precise.

TABLE 1: LINEARITY OF CANDESARTAN FOR THIRD ORDER

S.No.	Concentration ($\mu\text{g/ml}$)	D^2 value at detection wavelength (294.3 nm)
1	180	0.003
2	200	0.004
3	220	0.005
4	240	0.007
5	260	0.008
6	280	0.009

TABLE 2: INTRADAY PRECISION FOR THIRD ORDER

S.No	Concentration ($\mu\text{g/ml}$)	D^3 value at detection wavelength (294.3 nm)					Mean
		Time	I	II	III		
1	260	1:30 PM	0.008	0.008	0.008	0.008	
2	260	1:45 PM	0.008	0.008	0.009	0.00833	
3	260	2:00 PM	0.008	0.009	0.008	0.00833	
4	260	2:30 PM	0.009	0.008	0.008	0.00833	
5	260	3:30 PM	0.009	0.009	0.008	0.00866	
6	260	4:30 PM	0.008	0.009	0.009	0.00866	
Mean =						0.008	
SD =						0.00014	
% RSD =						1.75	

TABLE 3: TABLE 2 INTRADAY PRECISION FOR THIRD ORDER

S.No.	Concentration ($\mu\text{g/ml}$)	Days & Date	D^3 at 294.3 nm
1	260	8.4.2012	0.008
2	260	9.4.2012	0.008
3	260	10.4.2012	0.008
4	260	11.4.2012	0.008

5	260	12.4.2012	0.008
6	260	13.4.2012	0.009
	Mean =		0.008
	SD =		0.000135
	% RSD =		1.68

TABLE 4: ACCURACY STUDIES FOR THIRD ORDER

S.No.	Test ($\mu\text{g/ml}$)	Standard ($\mu\text{g/ml}$)	D ³ value at 294.3 nm	Conc. ($\mu\text{g/ml}$)	Amount of test recovered ($\mu\text{g/ml}$)	% Recovery
1	5	200	0.004	205	5	100
2	10	200	0.005	210	10	100
3	15	200	0.006	215	15	100

TABLE 5: DEPICTING THE ASSAY STUDY

S.no.	Conc. ($\mu\text{g/ml}$)	D ¹ value at 294.3 nm	% Purity (w/w)
1	220	0.007	100
2	220	0.007	100
3	220	0.007	100

CONCLUSION: The developed analytical method for Candesartan by using first order derivative spectroscopy is found to simple, rapid and selective and the amount of drug recovered will be same as the label claimed and precise. It can be conveniently employed for the routine analysis and quantification of Candesartan.

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