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Simultaneous Estimation of Candesartan Cilexetil and Hydrochlorthiazide in Tablet Dosage Form by UV Spectrophotometric Method

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Abstract: Candesartan cilexetil is a prodrug of candesartan which belongs to angiotensin II receptor blocker. Hydrochlorthiazide is a diuretic. Both of the drugs are used in treatment of hypertension. A simple, sensitive and reproducible UV Spectrophotometric method was developed using the solvent 0.1 N NaOH for simultaneous estimation of candesartan cilexetil and hydrochlorthiazide in tablet dosage form. Candesaratan cilexetil and hydrochlorthiazide exhibited absorbance at 251nm and 273nm in 0.1N NaOH and followed Beer's law in the concentration range of 4 – 28µg/ ml and 2 - 14µg/ml respectively. The results of analysis were validated statistically and by recovery studies confirmed the accuracy and precision of the method.

Keywords: *Candesartan Cilexetil; Hydrochlorthiazide; UV Spectrophotometry; simultaneous equation method, Method Validation.*

INTRODUCTION

Candesartan cilexexitil is a prodrug of candesartan. It is chemically 2-Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4-yl] -3Hbenzoimidazole-4-carboxylic acid 1 – cyclohexyloxycarbonyloxy ethyl ester used as an antihypertensive [(5)]. It inhibits the binding of angiotensin II to the AT_1 – receptor. Candesartan cilexetil is hydrolysed to candesartan in the gastrointestinal tract during absorption. Hydrochlorthiazide is a diuretic used as an antihypertensive. Chemically it is 6 – chloro – 3,4 dihydro – 2H – 1,2,4 – benzothiadiazine – 7 – sulfonamide 1,1 dioxide [(5)]. It inhibits the reabsorption of sodium and calcium at the beginning of distal convoluted. Literature survey revealed that a various analytical methods such as Q – Analysis, HPLC, HPTLC densitometry have been reported for the simultaneous estimation of both the drugs [(2), (3)]. The present investigation is an attempt to develop a simple, sensitive and reproducible UV Spectrophotometric method for analysis of tablet dosage form .

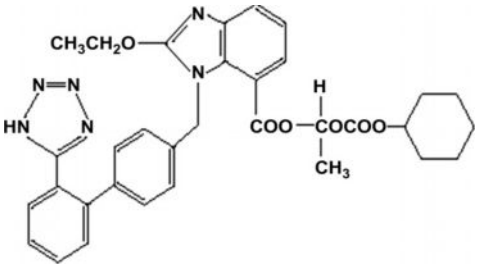


Fig.1. Chemical structure of candesartan cilexetil [(1)]

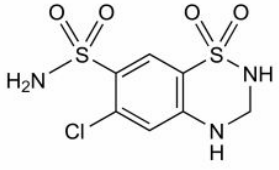


Fig.2.Chemical structure of hydrochlorothiazide [(1)]

MATERIALS AND METHODS:

Instruments:

Absorbance measurements was made on Shimadzu 1800 UV/Visible spectrophotometer with a pair of matched quartz cells of 1 cm width, Elder digital balance used for weighing, and Ultra sonicator of Prama instruments were used.

Chemicals and reagents:

All chemicals were of analytical reagent grade and solutions were prepared with purified water of I.P. grade. Candesartan cilexetil gift sample obtained from Dr. Reddy's Lab Hyderabad. Hydrochlorthiazide gift sample obtained from Emcure pharmaceuticals, Pune. Sodium hydroxide was purchased from Research-lab fine chem., Mumbai.

Procedure:

Sodium hydroxide solution (0.1M) was prepared by dissolving 2 gm of NaOH in distilled water and making the volume to 500 ml with distilled water to give 0.1M NaOH (4).

Candesartan cilexetil stock solution (1000 µg/ml) was prepared by dissolving 100 mg of accurately weighed candesartan cilexetil into a 100ml volumetric flask containing 50 ml of 0.1M NaOH. The solution was sonicated and the final volume was adjusted to 100 ml to give the stock solution of 1000µg/ml concentration. 10 ml of the resulting solution was placed in 100 ml volumetric flask and volume adjusted with 0.1M NaOH to give solution of 100µg/ml. Aliquots of 100µg/ml solution were suitably diluted with 0.1 M NaOH to give final concentrations of 4, 8, 12, 16, 20, 24, 28µg/ml.

Hydrochlorthiazide stock solution (1000 µg/ml) was prepared by dissolving 100 mg of accurately weighed hydrochlorthiazide into a 100ml volumetric flask containing 50 ml of 0.1M NaOH. The solution was sonicated and the final volume was adjusted to 100 ml to give the stock solution of 1000µg/ml concentration. 1 ml of the resulting solution was placed in 10 ml volumetric flask and volume adjusted with 0.1M NaOH to give solution of 100µg/ml. Aliquots of 100µg/ml solution were suitably diluted with 0.1 M NaOH to give final concentrations of 2, 4, 6, 8, 10, 12, 14µg/ml.

Procedure for calibration curve:

The λ_{max} of both the drugs in 0.1 N NaOH was found by UV spectrum in the range 200 – 400nm. It was to be 251 and 273 for candesartan cilexetil and hydrochlorthiazide respectively. The absorbance of prepared aliquots of 4, 8, 12, 16, 20, 24, 28 µg/ml candesartan cilexetil was measured against 251nm. While the absorbance of prepared aliquots of 2, 4, 6, 8, 10, 12, 14 µg/ml hydrochlorthiazide was measured against 273nm. (Spectral characteristics and linearity data is given in the table.)

Estimation of formulated tablets of Candesartan cilexetil:

20 formulated tablets of candesartan cilexetil and hydrochlorthiazide were triturated and powder equivalent to 16mg and 12.5mg of candesartan and hydrochlorthiazide respectively was weighed and transferred to 100 ml volumetric flask and volume adjusted upto the mark with 0.1 M NaOH. The solution was filtered through Whatman filter paper no 40. An aliquot containing 16 and 12.5 µg/ml of candesartan and hydrochlorthiazide respectively were analyzed by the above method (8).

Validation of the developed methods (9)

i) Linearity

For each drug, appropriate dilutions of standard stock solutions were assayed as per the developed methods. The Beer- Lambert's concentration range was found to be 2 - 14µg/mL and 2 - 28µg/mL for candesartan and hydrochlorthiazide respectively. The result of analysis is given in table1.

ii) Accuracy and Recovery studies

To check the accuracy of the proposed method, recovery studies were carried out 80, 100 and 120% of the test concentration as per ICH guidelines. The recovery study was performed three times at each level. The result of analysis is given in table 2.

iii) Precision:

Repeatability

To check the degree of repeatability of the methods, suitable statistical evaluation was carried out. Repeatability was performed for six times with tablets formulation. The standard deviation, coefficient of variation and standard error was calculated. The result of analysis is given in table.

Intermediate Precision (Interday and Intraday precision)

The interday and intraday precision was determined by assay of the sample solution on the same day and on different days at different time intervals respectively (six replicates).

RESULTS AND DISCUSSIONS:

Candesartan cilexetil and hydrochlorthiazide exhibited maximum absorption at 251 nm and 273 nm respectively. Candesartan cilexetil obeyed Beer's law in the concentration range of 4-28 µg/mL while hydrochlorthiazide obeyed the Beer's law in the concentration range of 2-14 µg/mL. Linear regression equation for candesartan cilexetil is Y=0.40035x-0.003 with a correlation coefficient of 0.999956 and for hydrochlorthiazide, linear regression equation is Y=0.066x-0.001 with a correlation coefficient of 0.999956. The percentage recovery revealed that the values lie within normal limit indicating that the proposed method is accurate. The method was proved to be rugged and robust.

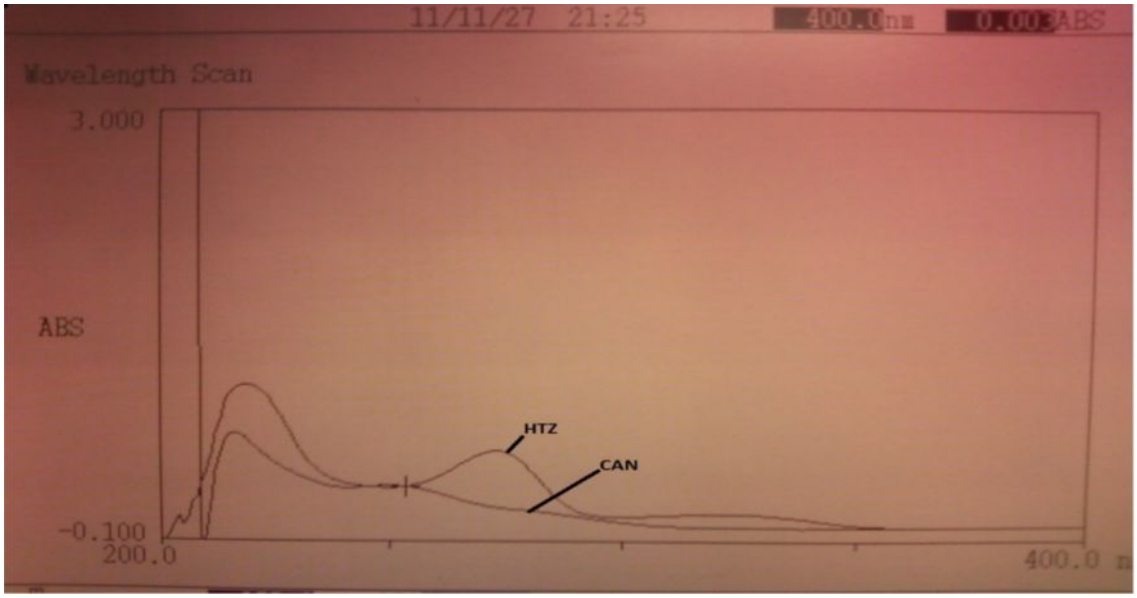
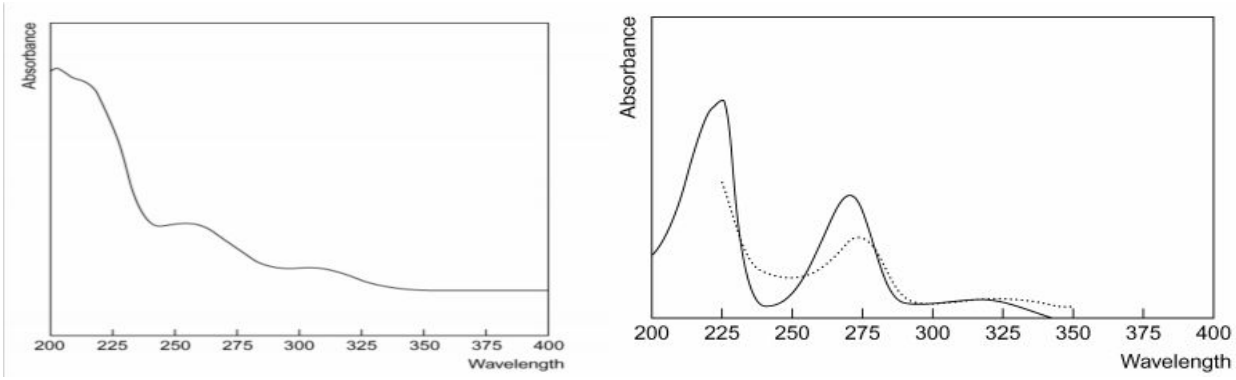


Fig.3. Scan of candesartan cilexitil and hydrochlorthiazide



Candesartan cilexetil **Hydrochlorthiazide**

Fig.4. Reference scans of candesartan cilexetil and hydrochlorthiazide (1)

Calibration curve of candesartan cilexetil and hydrochlorthiazide

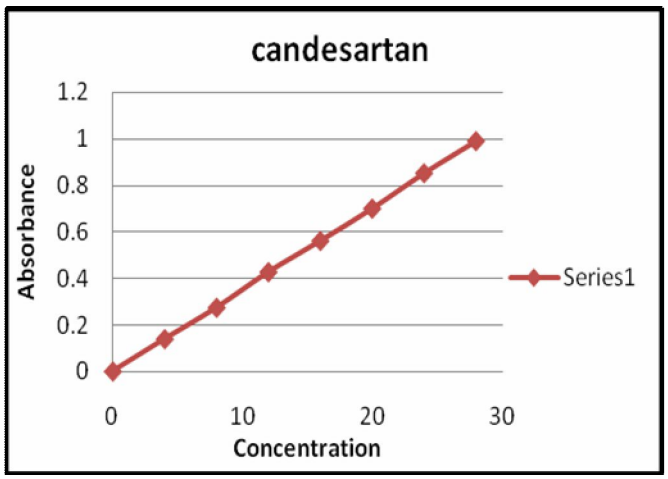


Fig.5. Calibration curve of candesartan cilexetil

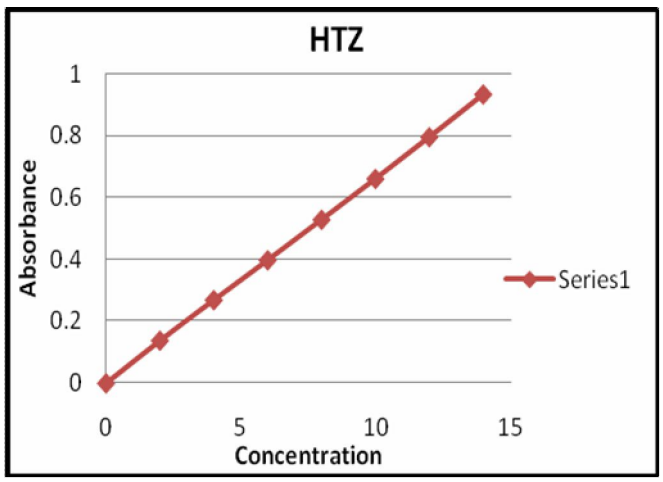


Fig.6. Calibration curve of hydrochlorthiazide

Table 1. Result of Validation parameters [9]:

Parameters	Candesartan	Hydrochlorthiazide
Detection wavelength	251 nm	273 nm
Beer's law limit	2-14 µg/mL	2-28 µg/mL
Slope	0.035438	0.06628
Intercept	-0.00325	-0.001667
Correlation coefficient	0.999956	0.999956
Regression equation (y =a + bc)	Y=0.035x-0.003	Y=0.066x-0.001
Limit of detection	0.571	0.300
Limit of quantitation	1.428	0.751

Table 2. Interday and Intraday precision [9]

	Interday precision		Intraday precision	
	%Amount found±SD*	% RSD	%Amount found±SD*	% RSD
Candesartan cilexetil	99.74±0.55	0.552190	99.68±0.374	0.37528
Hydrochlorthiazide	100.09±0.71	0.715624	99.52±0.241	0.243034

***Average of six determinations**

Table 3. Recovery studies (9):

Concentration of the drug added to the formulation	% Recovery ± SD*	
	Candesartan	Hydrochlorthiazide
80%	99.96±0.316	98.40±0.456
100%	99.54±0.441	101.22±0.336
120%	98.30±0.431	99.91±0.216

***Average of six determinations**

Table 4. Result of analysis of tablet formulation:

Formulation	Drug	Label Claim	Amount found ± S.D*	% label claim ±S.D*
Tablet	Candesartan	16 mg	15.97±0.150	99.81±0.93
	Hydrochlorthiazide	12.5 mg	12.41±0.105	99.28±0.84

***Average of three determinations**

CONCLUSION

A new, simple, sensitive spectrophotometric method was developed for the analysis of candesartan cilexetil and hydrochlorthiazide in bulk and in pharmaceutical formulation. The developed method was also validated and from the statistical data, it was found that method was accurate, precise, reproducible and can be successfully applied to the pharmaceutical formulation without interference of excipients.

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