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A VALIDATED NON-AQUEOUS POTENTIOMETRIC TITRATION METHOD FOR QUANTITATIVE DETERMINATION OF CANDESARTAN CILEXETIL FROM PHARMACEUTICAL PREPARATION

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ABSTRACT

A simple precise, rapid accurate and sensitive non-aqueous potentiometric titration method was developed for quantitative determination of candesartan cilexetil from pharmaceutical dosage form. The titration was carried out using standardized 0.1 N perchloric acid. The proposed method was found to be precise with % RSD < 1 (n = 6). The method showed strict linearity (r^2 > 0.9999) between 20% to 100% of 0.100 mg of drug substance weight. The percentage recovery of candesartan cilexetil in the optimized method was between 99.49 to 99.91%. The method is also found to be rugged when checked by different analysts and using different lots of reagents and different makes of titrators.

Key words: Candesartan cilexetil, Perchloric acid, Potassium hydrogen phthalate, Glacial acetic acid.

INTRODUCTION

Candesartan is an antihypertensive drug commercially available as cilexetil (cyclohexyl 1-hydroxy ethyl carbonate) ester form. It is a pro-drug and is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT1 subtype angiotensin II receptor antagonist. It is a non-peptide, chemically described as (±)-1-hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl) benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester) Candesartan cilexetil is white to off-white crystalline powder with a molecular weight of 610.67.

It is practically insoluble in water and soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, Candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, Candesartan. Literature survey reveals the spectrophotometric[1-4],

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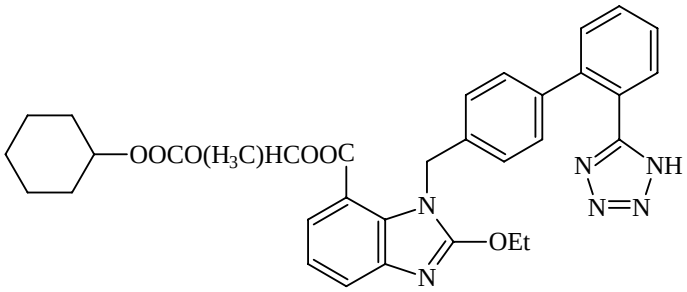
HPLC[5-11], UPLC[12] methods for the estimation of candesartan cilexetil. Simple, rapid and reliable UV spectrophotometric methods are developed for the determination of candesartan cilexetil. These methods can be used for the routine analysis. In the proposed methods optimization and validation of this method are reported.

Structure of candesartan cilexetil



EXPERIMENTAL

Instrumentation

An potentiometric titrator was used (Lab-India-TITRA*) with glass electrode (Sensorex) for assay method development and validation. A Simadzu analytical balance with 0.01 mg was used.

Reagents and chemical

Reference standard of candesartan cilexetil was obtained from reputed firm with certificate of analysis. Potassium hydrogen phthalate, perchloric acid and glacial acetic acid of A. R. grade were used.

General procedure

Standardization of 0.1 N perchloric acid

About 0.350 mg of potassium hydrogen phthalate (previously powdered lightly, dried at 120^{o}C for 2 hours) was weighed accurately into clean and dry titration jar. It was dissolved in 50 mL of glacial acetic acid. It was titrated with 0.1 N perchloric acid using auto titrator. Blank determination was performed out for necessary correction. The titration was performed in duplicate.

One mL of 0.1 N $HClO_4$ is equivalent to 0.2042 g of potassium hydrogen phthalate ($C_8H_5KO_4$)

$$\text{Normality of perchloric acid} = \frac{W}{B.R. \times 0.2042}$$

Where W is weight of potassium hydrogen phthalate in g.

B.R. is burette reading in mL.

Quantitative determination of Candesartan cilexetil

About 0.100 g. of candesartan cilexetil test sample was weighted accurately into a clean and dried titration jar. It was dissolved in 35 mL of anhydrous glacial acetic acid and 15 mL of 5% (w/v) mercuric acetate.

It was titrated with 0.1 N perchloric acid by auto titrator. Blank determination was also carried out for necessary correction. One mL of 1 N perchloric acid is equivalent to 0.07719 g. of candesartan cilexetil % (Percentage) Candesartan cilexetil on the dried basis was calculated as below.

$$\% \text{ assay} = \frac{B.R. \times N \times 0.10177 \times 100}{W}$$

Where B.R. is burette reading in ml at the potentiometric end point.

N is actual normality of 0.1 N perchloric acid.

W is weight of the sample taken in g.

RESULTS AND DISCUSSION

Determination of candesartan cilexetil

The objective of this work was to determine accurately the content of candesartan cilexetil. The assay of candesartan cilexetil (on the dried basis) of various batches of candesartan cilexetil test sample was analyzed using the above method. It was in the range of 99.76% to 100.07%.

Analytical method validation

The method precision was checked after analyzing six different preparations of homogeneous test sample of candesartan cilexetil. The % RSD of results obtained was found to be 0.6743. It confirms good precision of the method. The results are presented in Table 1.

Table 1: Method of precision

S. No.	Weight of candesartan cilexetil	Burette reading in mL	Normality of perchloric acid	% Assay
1	0.100	9.83	0.09994	99.97
2	0.100	9.81	0.09994	99.76
3	0.100	9.82	0.09994	99.86
4	0.100	9.84	0.09994	100.07
5	0.100	9.83	0.09994	99.97
6	0.100	9.82	0.09994	99.86
			Mean	99.915
			Std. Deviation	0.109681
			RSD	0.109775

Linearity

For the establishment of method linearity, five different weights of candesartan cilexetil test samples corresponding to 20%, 40%, 60%, 80% and 100% of the about weight (0.100 g) were taken and analyzed for % (percentage) of candesartan cilexetil content. The results are in Table 2.

Table 2: Linearity

S. No.	Weight of candesartan cilexetil	Burette reading	Normality of perchloric acid	% Assay
1	0.020	1.96	0.09990	99.67
2	0.040	3.93	0.09990	99.92
3	0.060	5.88	0.09990	99.66
4	0.080	7.84	0.09990	99.67
5	0.100	9.83	0.09990	99.87
			Mean	99.758
			Std. Deviation	0.126372
			RSD	0.126679

The potentiometric titration was conducted once at each level. Linearity curve Fig. 1 was drawn by plotting test sample weight in gram on x axis and titre values on y axis.

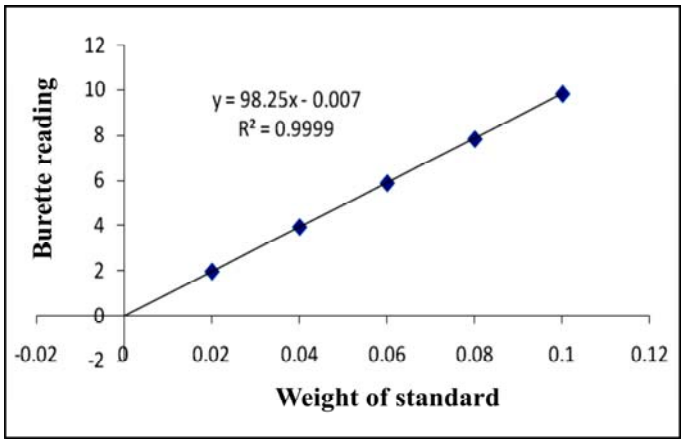


Fig. 1: Linearity curve

The values of correlation coefficient, slope and intercept are given in table 3.

Table 3: Regression values

Parameter	Values
Slope	98.25
Intercept	-0.007
Coefficient of co-relation	0.9999

Accuracy and recovery

Accuracy was determined at five different levels i.e., 20%, 40%, 60%, 80% and 100% of the nominal concentration (0.100 g). The titration was conducted in triplicate at each level and the titre value was recorded. The tire value obtained in linearity study was considered as true value during the calculation of percentage (%) recovery. The percentage recovery is calculated using following equation.

$$\text{Percentage recovery} = \frac{\text{Titre value} \times 100}{\text{True titre value}}$$

The percentage range recovery of candesartan cilexetil was in 99.49 to 99.91 %. It confirms the accuracy of the proposed method (Table 4).

Table 4: accuracy and precision

Level No.	Weight of candesartan cilexetil added	Burette reading	Weight of candesartan cilexetil found	% Assay	Mean % assay
1	0.020	1.96	0.0199	99.67	99.66
	0.020	1.97	0.0200	100.17	
	0.020	1.95	0.0198	99.15	
2	0.040	3.93	0.0399	99.92	99.91
	0.040	3.92	0.0398	99.66	
	0.040	3.94	0.0401	100.17	
3	0.060	5.88	0.0597	99.66	99.49
	0.060	5.87	0.0596	99.49	
	0.060	5.86	0.0595	99.32	
4	0.080	7.84	0.0797	99.67	99.66
	0.080	7.85	0.0798	99.79	
	0.080	7.83	0.796	99.53	
5	0.100	9.83	0.0999	99.97	99.86
	0.100	9.81	0.0997	99.76	
	0.100	9.82	0.0998	99.86	

Ruggedness

The ruggedness of the method is defined as degree of reproducibility of results obtained by analysis of candesartan cilexetil sample under variety of normal test conditions such as different laboratories, different analysts and different lots of reagents. Quantitative determination of candesartan cilexetil was conducted potentiometrically on one laboratory. It was again tested in another laboratory using different instrument by different analyst. The assays obtained in two different laboratories were well in agreement. It proved ruggedness of the proposed method.

CONCLUSION

The proposed method of non-aqueous potentiometric titration was found to be precise, accurate and rugged. The values of percentage recovery and standard deviation

showed sensitivity. The method was completely validated. It showed satisfactory data for all the parameters of validation. Hence, it can be applied for routine quality control application.

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