

Research Article

Sensitive and Simple Spectrophotometric Methods for Determination of Candesartan Cilexetil in Bulk and Pharmaceutical Dosage Forms

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Two new rapid, simple, sensitive reproducible and economical spectrophotometric methods are described for the determination of Candesartan cilexetil (CDC) in bulk form. Both methods are based on the formation of colored complexes due to the action of Safranin-O and MethyleneBlue on CDC in alcoholic medium. Under optimized conditions, they show an absorption maxima at 520 nm (SFN-O) and 650nm (MB), with molar absorptivities of 3.685×10^4 and 3.096×10^4 mole⁻¹ cm⁻¹ and sand ells sensitivities of 0.06329 and 0.02575 per 0.001 absorbance unit for SFN-O and MB, respectively. The color is stable for 5 min after extraction. Beers law is obeyed between 2.0-10.0 µg/ ml for SFN-O and 2.0-10 µg/ ml for MB. The proposed methods were successfully extended to bulk and Pharmaceutical dosage forms.

Keywords: Candesartan cilexetil (CDC), Safranin-O (SFN-O), and MethyleneBlue (MB), Spectrophotometry, Ion association complex

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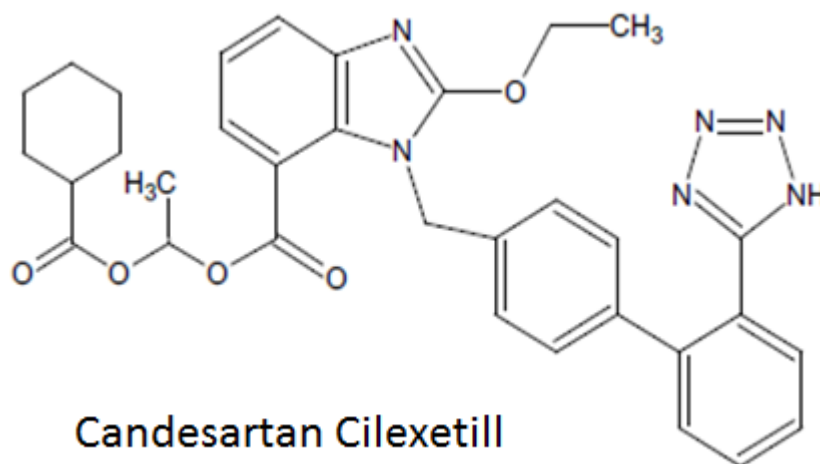
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Introduction

Candesartan cilexetil belongs to the class of angiotensin receptor antagonists and acts by competitively to angiotensin II receptor type I, thus preventing actions of angiotensin II. The drug finds most significant clinical use in the treatment of hypertension of all grades [1]. Chemically, candesartan cilexetil is an ester prodrug of its active metabolite candesartan (C.V. 11974), to which it owes its therapeutic effect, by the action of some endogenous esterases [2]. The chemical stability of Candesartan cilexetil has been studied in plasma and bioanalytical samples [3]. Under these conditions the drug was found to be susceptible to hydrolysis resulting the removal of cilexetil moiety. Few methods for the determination of Candesartan cilexetil have been reported in literature. HPLC methods were reported for determination of Candesartan cilexetil with some angiotensin II receptor antagonists with or without hydrochlorothiazide as a diuretic drug [4-6]. Also, HPLC methods were reported for determination of Candesartan cilexetil in tablets, as a single component [3, 7-9], in combination with Candesartan and a metabolite (M II) [10] in human plasma and urine and with hydrochlorothiazide simultaneously in pharmaceutical formulations [11-13]. Capillary electrophoresis methods were reported for simultaneous analysis of several angiotensin II receptor antagonists including Candesartan cilexetil [14-17]. Other methods such as voltametry [18-20] and HPTLC densitometry [21] were reported for determination of Candesartan cilexetil. The only spectrophotometric methods reported for determination of Candesartan cilexetil were the first order derivative for it in tablets [22] as a single component or simultaneously with hydrochlorothiazide [23] or for simultaneous determination of Candesartan and hydrochlorothiazide in tablets [24].

Very few spectrophotometric methods have been reported for estimation of Candesartan cilexetil in tablet dosage form. Its empirical formula is C₃₃H₃₄N₆O₆, Molecular weight is 610.7 and its structural formula is:



In the present investigation an attempt was made to develop simple and economical spectrophotometric methods with greater precision, accuracy and sensitivity for the analysis of Candesartan cilexetil in bulk and pharmaceutical formulation.

Experimental

All spectral measurements were made on ELICO SL-159 double beam UV-Visible spectrophotometer. An ELICO LI-120 Digital pH meter was used for pH measurements.

Preparation of reagents

Candesartan cilexetil Stock solution

The stock solution (1mg/mL) of candesartan cilexetil was prepared by dissolving 100mg of it in 10mL of methanol, followed by dilution to 100mL with distilled water.

Safranin O Solution: (Fluka; 0.2%, w/v $5.714 \times 10^{-3}M$)

Prepared by dissolving 200 mg of Safranin O in 100mL of distilled water and subsequently washed with chloroform to remove chloroform soluble impurities.

MB solution: (Fluka; 0.2%, w/v $6.25 \times 10^{-3}M$)

Prepared by dissolving 200mg of MB in 100mL of distilled water and subsequently washed with chloroform to remove chloroform soluble impurities.

Buffer solution p^H 9.8: ($NH_4OH - NH_4Cl$)

7gms of NH_4Cl and 6.8mL of liquid Ammonia solutions were mixed and diluted to 100mL with distilled water and pH was 9.8.

Method A& B

Aliquots of standard drug (CDC) solution (0.5 - 2.5mL for method A and 0.5-3.0mL, for method B $50 \mu\text{g}\cdot\text{mL}^{-1}$) and 1.0mL of p^H 9.8 buffer solution were placed separately in a series of 125mL separating funnels. A Volume of 1.0mL of Safranin-O (for method A), 0.5mL of MB (for method B) were added respectively. The total volume of aqueous phase in each funnel was adjusted to 10.0mL with distilled water. Then 10.0mL of chloroform was added in each separating funnel and the contents were shaken for 2min and allowed to separate. The organic layer was collected through cotton plug and the absorbance was measured immediately at 520nm (for method A) and at 650nm (for method B) against a reagent blank. All the colored species were stable for 2 hours. The amounts of drug (CDC) in sample solutions for both the methods were calculated from the Beer's Lambert plots shown in figure 1&2.

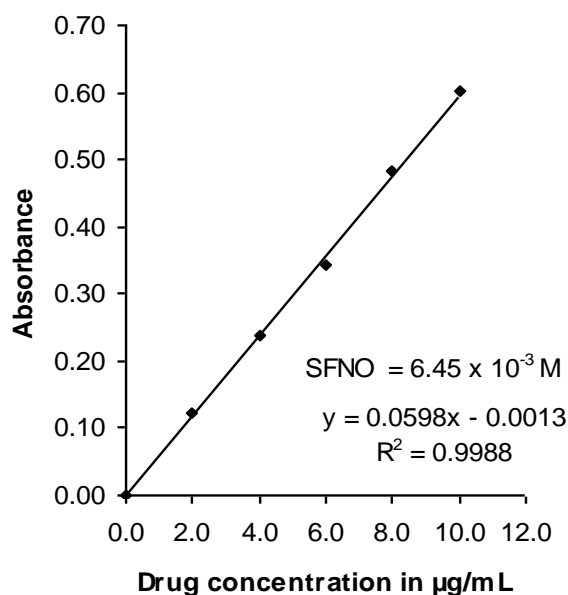


Figure 1 Beer's Law plot of CDC with SFN-O (Method-A)

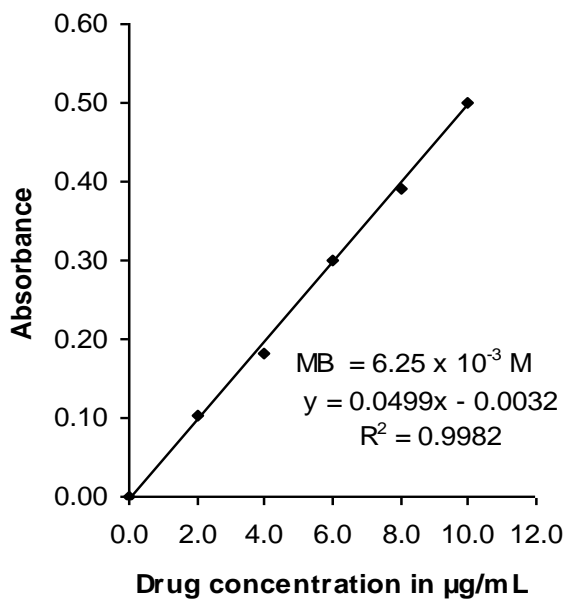


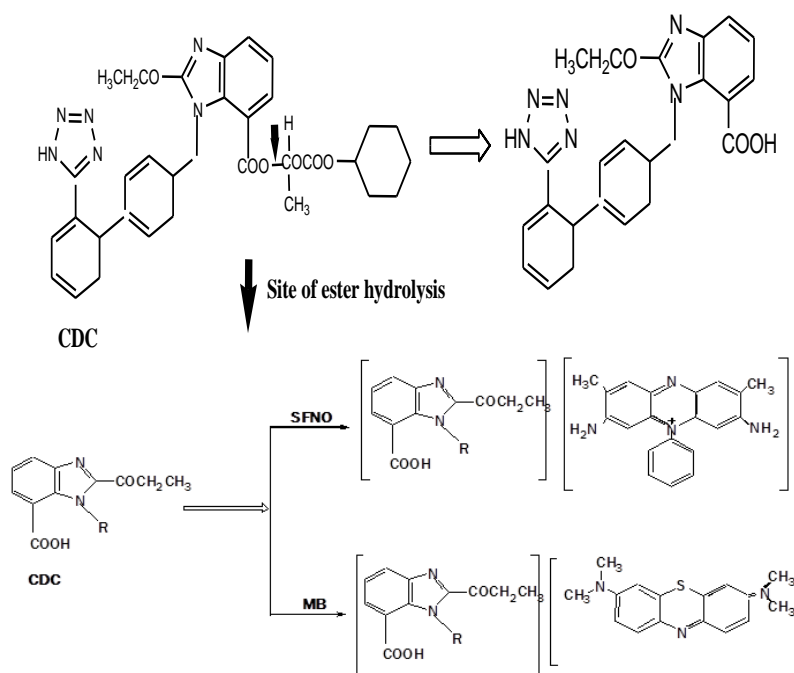
Figure 2 Beer's Law plot of CDC with MB (Method-B)

Procedure for the assay of CDC in formulations

An accurately weighed portion of powdered tablets equivalent to 100mg of CDC was dissolved in 20mL of methanol (MeOH), shaken well and filtered, the filtrate was diluted to 100mL with MeOH to get 1mg/mL of drug in formulations. 0.5mL of this solution was diluted to 100mL to get 5µg/mL. The absorbance of the solution was determined at 212nm. The quantity of was computed from Beers law of standard drug in MeOH.

Nature of color species

CDC upon hydrolysis possesses carboxyl group (acidic), is responsible for color formation in ion association complex with basic dyes (Saffranin- O and Methylene blue), which is extractable into chloroform from aqueous phase. The carboxylate anion (negative charge) of CDC is expected to attract the oppositely charged part of the dye [positive charge, Safranin O (Method-A) and Methylene blue (Method-A) and behave as single unit being held together by electrostatic attraction.



Results and Discussion

The optical characteristics such as absorption maxima, Beer's law limits, molar absorptivity and sand ell's sensitivity are presented in **Table 1** the regression analyses using the method of least squares were made for the slope. (b) Intercept (a) and correlation(r) obtained from different. Concentrations and the results are summarized in Table 1. The present relative Standard deviation and percent range of error (0.05 and 0.01 confidence limits) calculated from the six measurements $\frac{3}{4}$ of the upper Beer's law limits of Candesartan cilixetil are given in Table 1. The results showed that these methods have reasonable precision. Comparison of the results obtained with the proposed and UV methods for dosage forms (**Table 2**) confirm the suitability of these methods for pharmaceutical dosage forms. In order to justify the reliability and suitability of the proposed methods, known quantities of pure Candesartan cilixetil was added to its various preanalysed formulations and the mixture were analyzed by the proposed methods. The results of recovery experiments were analyzed by the proposed methods the results of recovery experiments are also summarized in Table 2. The other active in gradients and excipients usually present in pharmaceutical dosage forms did not interfere.

Table 1 Optical characteristics, precision, accuracy of the methods proposed in the determination of Candesartan cilixetil

S.NO	Optical characteristics	SFN-O	MB
1	λ_{\max} (nm)	520	650
2	Beer's law limits($\mu\text{g/ml}$)	2.0-10.0	2.0-10.0
3	Molar Absorptivity ($\text{mol}^{-1}\text{cm}^{-1}$)	3.685×10^4	3.096×10^4
4	Correlation coefficient(γ)	0.9988	0.9982
5	Sandell's Sensitivity ($\mu\text{g/cm}^2/0.01$ absorbance unit)	0.06329	0.02575
6	Regression equation ($y=a+bC$)		
	(i)Slope(b)	0.0598	0.0499
	(ii)Intercept (a)	0.0013	0.0032
7	Relative standard deviation*	0.479	0.570
8	% of range error (confidence limit)		
	0.05level	0.503	0.598
	0.01level	0.789	0.938

*Average of six determinations considered

Analysis of formulations

Commercial formulations (tablets) containing CDC were successfully analyzed by the proposed methods. The values obtained by the proposed and reference method (UVmethod) for formulations were compared statistically with F and t tests and found not to differ significantly. The results of the recovery experiments by the proposed methods are also listed in Table 2.

Table 2 Assay of CDC in Pharmaceutical Formulations

Formulations*	Amount taken (mg)	Amount found by proposed Methods**		Reference method	Percentage recovery by proposed methods***	
		Method-A	Method-B		Method-A	Method-B
Tablet I	4	3.92±0.11 F=2.11 t=0.513	3.89±0.09 F=3.16 t=0.96	3.96±0.16	97.95±0.90	96.42±0.95
Tablet II	8	7.97±0.03 F=4.0 t=0.38	7.95±0.05 F=1.70 t=1.38	7.98±0.06	99.48±0.98	96.96±0.90

- Tablets from four different pharmaceutical companies.
- Average \pm standard deviation of six determinations, the t- and F-test values refer to
 - comparison of the proposed method with the reference method. Theoretical values at 95%
 - confidence limit, F = 5.05, t = 2.262
- Recovery of 10mg added to the preanalysed pharmaceutical formulations (average of three determinations)

Conclusion

The present work is concerned with the determination of candesartan cilexetil in bulk and pharmaceutical dosage forms. In this work simple, sensitive and rapid methods are described for determination of candesartan cilexetil in pure form or in pharmaceutical formulations. From the results obtained, it is concluded that the suggested methods showed high sensitivity, accuracy, specificity and reproducibility and can be used as stability indicating method.

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