Determination of Candesartan Cilexetil in Bulk and Pharmaceutical Dosage Forms by Visible Spectrophotometric Methods

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Abstract: *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 2, 6-Dichloroquinone chlorimide (DCQC) and 1, 2 Napthaquinone, 4- Sulphonic acid (NQS) on CDC in alcoholic medium. Under optimized conditions, they show an absorption maxima at550 nm (DCQC) and 480nm (NQS), with molar absorptivities of 1.237×10^4 and 3.366×10^4 mole- cm- and sand ells sensitivities of 0.06329 and 0.1578 per 0.001 absorbance unit for DCQC and NQS , respectively. The color is stable for 5 min after extraction. Beers law is obeyed between 5.0-25.0 µg/ ml for DCQC and 4.0-20 µg/ ml for NQS. The proposed methods were successfully extended to bulk and Pharmaceutical dosage forms.*

Keywords: Candesartan cilexetil (CDC), 2, 6-Dichloroquinone chlorimide (DCQC), 1, 2 Napthaquinone, 4- Sulphonic acid (NQS), Spectrophotometry, Oxidative coupling.

1. Introduction

Candesartan cilexetil (CDC) is Angiotensin II receptor Antagonist. It is used in antihypertensive. Chemically it is 2-Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl]-3Hbenzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy ethyl ester [1].The typical dose of Candesartan cilexetil is 16 mg per day in patients who are not volume depleted. It may be given once or twice daily with total daily doses ranging from 8 mg to 32mg [2]. Candesartan cilexetil is hydrolyzed to Candesartan during absorption from the gastrointestinal tract [3].Tablet formulation containing 4 mg and 8 mg Candesartan cilexetil are available in market. Literature survey revealed that various analytical methods such as Q-Analysis spectrophotometric method for estimation of Candesartan cilexetil and Hydrochlorothiazide in tablet dosage form [4].HPTLC-densitometric analysis of and Hydrochlorothiazide in tablets [5].HPLC, RP-HPLC, and LC-UV methods are used estimation of Candesartan cilexetil [6-8].

Very few spectrophotometric methods have been reported for estimation of Candesartan cilexetil in tablet dosage form. Its empirical formula is $C_{33}H_{34}N_6O_6$, Molecular weight is 610.7 and its structural formula is:
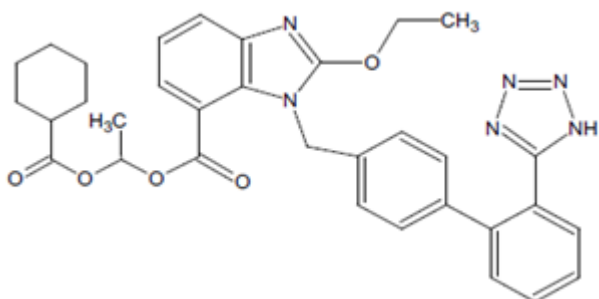
Candesartan Cilexetill

In the present investigation an attempt was made to develop a simple and economical spectrophotometric method with greater precesion, 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 cilexetill Stock solution:

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

DCQC Solution (BDH; 0.04%, 1.9×10^{-3}M): Prepared by dissolving 40mg of DCQC in 100mL of isopropanol.
NQS solution (Loba; 0.5%, 1.92×10^{-2}M): Prepared by dissolving 500mg of NQS in 100mL of distilled water.
NaOH solution (E.Merck; 20%, 5M): Prepared by dissolving 20gm of sodium hydroxide in 100mL of distilled water.

Method-A:
Into a series of 25ml calibrated tubes, aliquots of standard CDC solution (0.5 - 3.0mL, 200µg.mL^{-1}) were transferred. Then 5.0mL of buffer (pH 9.4) and 2.0mL (1.9×10^{-3}M) of DCQC were added successively. The contents were mixed well and kept aside for 10min and diluted to mark with

distilled water. The absorbance of the colored solution was measured at 550nm against a reagent blank prepared simultaneously. The amount of CDC in the sample solution was computed from the appropriate calibration graph.

Method-B:

Aliquots of standard CDC solution (0.5 – 3.0mL; $100\mu g.mL^{-1}$) were transferred into a series of 10mL calibrated tubes containing 0.2mL of 0.02N NaOH and 0.2mL (1.92×10^{-2}M) of NQS reagent solution was added in each tube and the contents were heated at 50^0c for 5min and cooled for 2min in ice water. This operation was performed in the dark. After cooling, the contents in the tube were rinsed with 1.0mL of water. Then 0.5mL of con H_2SO_4 was added slowly, mixed and the absorbance were measured after 5min at 480nm against a reagent blank prepared similarly. The amount of CDC was calculated from its calibration graph.
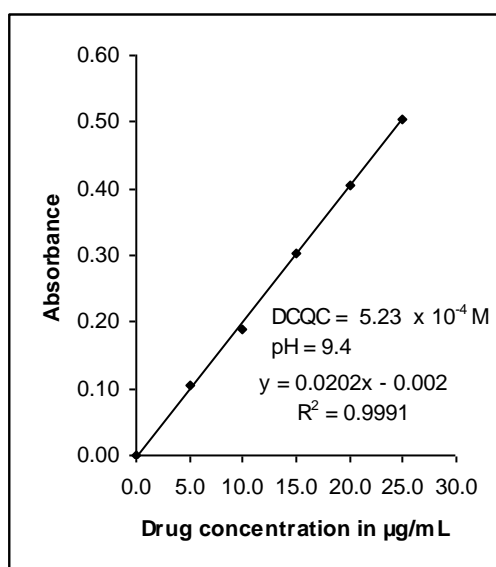

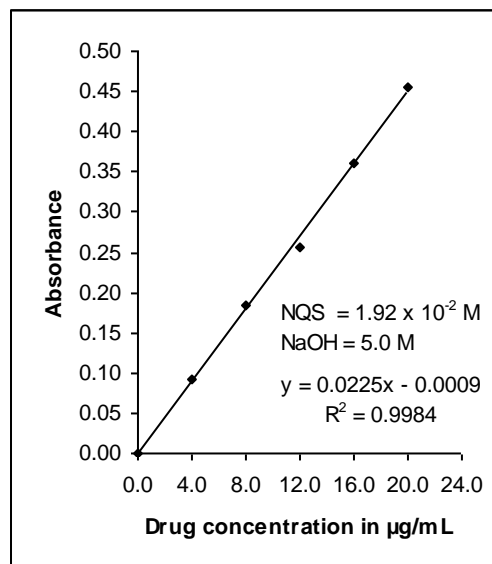**Figure 1:** Beer's Law plot of CDC with DCQC (Method-A).

**Figure 2:** Beer's Law plot of CDC with NQS (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 100mLwith MeOH to get 1mg/mLof 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

It is difficult to predict the exact nature of colored species formed in the proposed methods. The reviews concerning the reagents used for color development by exploiting appropriate functional moieties in CDC (such as secondary amine, tertiary amine, sulphur and and keto groups of varied reactivity were presented). An attempt has been made to indicate the nature of colored species in each of the proposed methods for CDC is tentatively based on analogy (reactive functional moiety in drug, reagents nature).Secondary amine in CDC was responsible for the development of Oxidative coupling with2, 6-Dichloroquinone chlorimide (DCQC), 1, 2 Napthaquinone, 4- Sulphonic acid (NQS).

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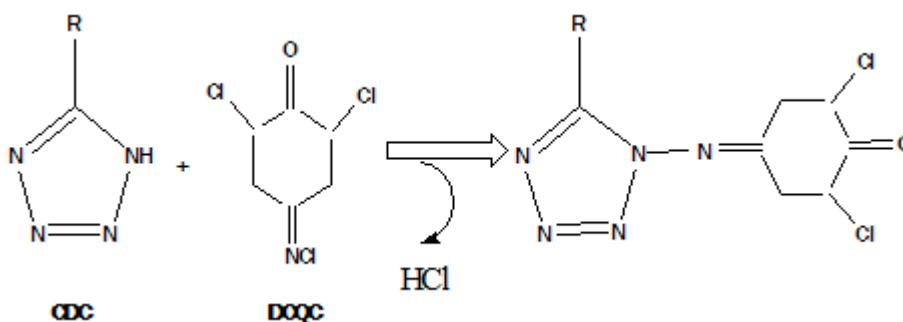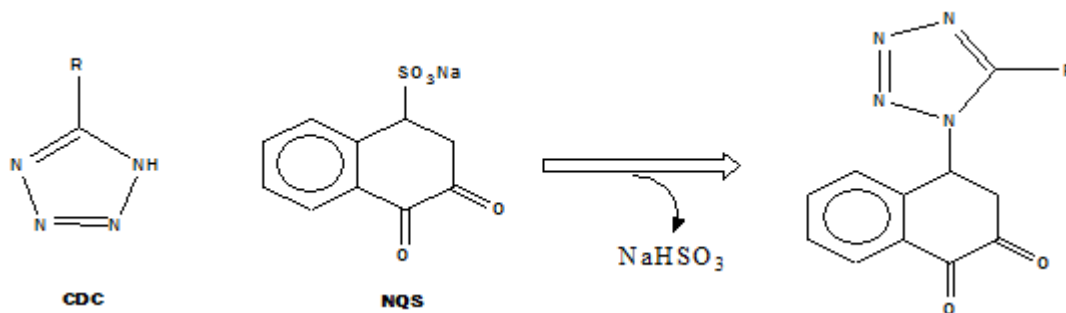
2. Results and Discussion

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 ¾ of the upper Beer's law limits of Candesartan cilexetill 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 cilexetill was added to its various preanlysed 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 execipients usually present in pharmaceutical dosage forms did not interfere.

3. 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 different significantly.

The results of the recovery experiments by the proposed methods are also listed in Table- 2.

4. Conclusion

The proposed methods are found to be simple, sensitive selective, accurate and economical when compared to quantitative methods by HPLC and LC-MS. It can be used in the determination of Candesartan cilexetil in bulk drug and its pharmaceutical dosage forms in a routine manner.

5. Acknowledgements

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

S.NO	Optical characteristics	DCQC	NQS
1.	λ_{max}(nm)	550	480
2.	Beer's law limits(μg/ml)	5.0-25.0	4.0-20.0
3.	Molar Absorptivity (mol^{-1}cm^{-1})	1.237×10^4	3.366×10^4
4.	Correlation coefficient(γ)	0.9991	0.9984
5.	Sandell's Sensitivity (μg/cm^2/0.01absorbance unit)	0.06329	0.1578
6.	Regression equation(y=a+bC) (i)Slope(b) (ii)Intercept (a)	0.0202 0.002	0.0225 0.0009
7.	Relative standard deviation∗	0.570	0.536
8.	% of range error (confidence limit) 0.05level 0.01level	0.598 0.938	0.562 0.882

∗Average of six determinations considered

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 ± 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)

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