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VALIDATED SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF DOXAZOCIN IN PURE AND IN ITS DOSAGE FORM

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ABSTRACT

A simple, precise, rapid, sensitive and accurate Spectrophotometric methods have been developed for the estimation of Doxazocin UV in pure form and its pharmaceutical formulations based on oxidative complexation reaction UV with 1.10- phenanthroline reagent at P^H- 4 which is extractable at 510nm. Beer's law is obeyed in the concentration range 1-6ml (10 to 60µg ml^{-1}). The developed method was applied directly and easily for the analysis of the pharmaceutical formulations. RSD was found to be 0.5318 and recovery 99.77 % respectively. The method was completely validated and proven to be rugged. The interferences of the ingredients and excipients were not observed. The repeatability and the performance of the proved method were established by point and internal hypothesis and through recovery studies.

KEYWORDS

Spectrophotometry, Doxazocin, 1, 10-phenanthroline and Oxidative complexation.

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INTRODUCTON

Doxazosin [(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-(1, 4-benzodioxan-2-yl-carbonyl) piperazine] is a postsynaptic α 1-adrenoreceptor antagonist used either alone or in combination with diuretics or α1-adrenergic-receptorant agonist for the treatment of hypertension and benign prostatic hyperplasia. It is structurally related to prazosin Figure No.1. The literature survey of Doxazosin as follows. Babmoto *et al*[1], Eliot *et al*[2], and Carlson *et al* and Bailey *et al*[3], has to Report the analysis of pharmacokinetics and effect on blood pressure of Doxazosin in normal subjects and patients.

Cowlishaw *et al*[4], has to describe HPLC with Fluorescence detection for Doxazosin determination. HPNC analysis of Doxazosin has been reported in human serum and roboticsamples[5-10]. X. Wat, *et al*, have been reported for the analysis of Doxazosin by Solid-Phase extraction[11]. Ma *et al*[12], has been described Mass spectrophotometry for analysis of Doxazosin. Validation of Doxazosin by HPLC in human serum and food determined by UV-Vis spectrophotometric method[13-19], Volummetric methods[20-29].

In the present study an attempt has been made to develop simple UV-Vis spectrophotometric method for quantitative estimation of Doxazosin in its technical grade formulations and biological sample (blood). The functional group used for the color development of Doxazosin was primary amine. The result obtained in this method was based on complexation reaction formation reaction of Doxazosin with 1, 10-phenanthroline. The empirical formula for Doxazosinmesylate is $C_{23}H_{25}N_5O_5$ and the molecular weight is 451.47 grams. It has the following structure.

There is however no reported UV- Vis spectrophotometric method for the analysis of Doxazosinin its technical grade and formulations. In the present study an attempt has been made to develop simple UV-Vis spectrophotometric method for the quantitative determination of Doxazosin. Functional group used for color development of Doxazosin was primary amine group. The results obtain in this method was based on oxidative complexation reaction with 1, 10-PT. An attempt has been made to develop and validate all methods to ensure their accuracy, precision, repeatability, reproducibility and other analytical method validation parameters as mentioned in the various guidelines.

MATERIAL AND METHODS

Pure sample

The pure sample was collected from CIPLA pharmaceuticals. Avalahalli, Vigro agar, Bangalore, 560049.

Preparation of standard calibration curve of pure drug

Solvent

Dimethylsulfoxide was used as solvent.

Preparation of standard stock solution

Accurately weighed 100 mg of Doxazosin was dissolved in 40 ml of Dimethylsulfoxide in 100ml volumetric flask and volume was made up to the mark with Dimethylsulphaoxide. i.e. 1000µg ml^{-1} (Stock solution A). Twenty tablets containing Doxazosinmesylate were weighed and From the above stock solution A 10ml was pipette out into 100ml volumetric flask and the volume was made up to the mark with Dimethylsulfoxide to obtain the final concentration of 100µg ml^{-1} (Stock solution B)

Preparation of Calibration curve

Fresh aliquots of ranging from 1 to 6ml were transferred into a series of 10ml volumetric flasks to provide final concentration range of 10 to 60 (µg ml^{-1}). To each flask 1ml of (0.01M) 1, 10-phenanthroline solution was added followed by 1ml of (0.2%) Ferric chloride solution and resulting solution was heated for 15 min and finally 1ml (0.2M) Ortho phosphoric acid solution was added. The solutions were cooled at room temperature and made up to mark with distilled water. The absorbance of orange red colored chromogen was measured at 510 nm against the reagent blank. The color species was stable for 24 h. The amount of Doxazosin present in the sample solution was computed from its calibration curve.

Procedure for formulations

An accurately weighed portion of the powder equivalent to 100mg of Doxazosin was dissolved in 100 ml of Dimethyl sulfoxide and mixed for about 5min and then filtered. The Dimethyl sulfoxide was evaporated to dryness. The remaining portion of solution was diluted in 100 ml volumetric flask and made up to 100 ml to get the stock solution A. 10ml of aliquots was pipette out into 100ml volumetric flask and the volume was made up to the mark with Dimethylsulfoxide to obtain the final concentration of 100µg ml^{-1}(Stock solution B).

Subsequent dilutions of this solution were made with Dimethylsulfoxide to get concentration of 10 to 60µg ml^{-1} and were prepared as above and

analyzed at the selected wavelength, 510nm and the results were statistically validated.

Procedure for Blood sample

After collection of blood sample it will be centrifuged. For isolation of Doxazosin from plasma sample, Dimethylsulfoxide was used for protein precipitation. Liquid- Liquid extraction was performed with plasma by alkalinization with 1M NaOH, followed by extraction with 30% dichloromethane in Hexane. The upper organic layer was evaporated to dryness and the dry residue 100mg was dissolved in 100 ml of Dimethylsulfoxide (1000µgml^{-1}). From the above solution 10ml is taken into a 100ml volumetric flask and made up to the mark (100µg ml^{-1}).

From the above solution ranging from 1- 6ml (10-60µg ml^{-1}) were transferred in to 10ml volumetric flask and to the each flask 1ml of (0.01M) 1, 10-phenanthroline solution was added followed by 1ml of (0.2%). Ferric chloride solution and made up to the mark. Then the resulting solution was heated for 15 min and finally 1ml (0.2M) Orthophosphoric acid solution was added. The solutions were cooled at room temperature and made up to the mark with distilled water. The absorbance of orange red colored chromogen was measured at 510nm against reagent blank. The color species was stable for 24 h. The amount of Doxazosin present in the sample solution was computed from calibration curve.

RESULTS AND DISCUSSION

Optical parameters

In order to ascertain the optimum wavelength of maximum absorption (λ_{max}) formed in UV spectrophotometric method (Reference method – A) and the colored species formed in each four visible spetrophotometric methods, specified amount of Doxazosin in final solution 10µg ml^{-1}is taken and the colors were developed. The absorption spectra were recovered on spectrophotometer in the wavelength region of 380-800 nm against corresponding reagent blanks. The regent blank absorption spectrum of each method was also recorded against distilled water (or) Dimethylsulfoxide. The results are graphically represented.

Parameters fixation

In developing these methods, a systematic study of the effects of various relevant parameters in the methods concerned were under taken by verifying one parameter at a time and controlling all other parameters to get the maximum color development for this method. Reproducibility and reasonable period of stability of final colored species formed. The following studies were conducted.

METHODS

The results obtained in this method were based on oxidation followed by complex formation reaction of Doxazosin with 1,10-phenanthroline, Ferric chloride and Orthophosphoric acid to form an orange red colored chromogen that exhibited maximum absorption at 510 nm against the corresponding reagent blank. The functional group used for the color development for this method was primary amine group. A schematic reaction mechanism of Doxazosin with 1, 10-Phenanthroline reagent was shown in Figure No.4. The effect of various parameters such as concentration and volume of 1, 10- Phenanthroline and strength of acid order of addition of reagents, solvent for final dilution were studied by means of control experiments varying one parameters at a time.

Optical characteristics

The reference method adhere to Beer's law the absorbance at appropriate wave length of a set of solutions contains different amounts of Doxazocin and specified amount of reagents (as described in the recommended procedure) were noted against appropriate reagent blank. Least square regression analysis was carried out for the slope. Intercept and correlation coefficient, Beer's law limits, molar absorptivity and sandells sensitivity for Doxazocin with each of mentioned reagents was calculated. In order to test whether the colored species formed in the method adhere the Beer's law the absorbance at appropriate wavelength of a set of solutions contain different amounts of Doxazocin and specified amount of reagents (as described in the recommended procedure) were noted against appropriate reagent blanks or distilled water. The Beer's law plots of the system illustrated

graphically in Figure No.3 and No.4 least square regression analysis was carried out for the slope, intercept and correlation coefficient, Beer's law limits molar absorptivity Sandells sensitivity for Doxazocin with each of mentioned reagents were calculated. The optical characteristics are represented in the Table No.1.

PRECISION

The precision of each one among the five proposed spectrophotometric methods were ascertained separately from the absorbance values obtained by actual determination of a fixed amount of Doxazosin (5, 4, 10 and 5µg ml^{-1} respectively - A, B, C and D) in final solution. The percent relative standard deviation and percent range of error (at 0.05 and 0.01 confidence limits) were calculated for the proposed methods and presented in Table No.1.

Analysis of formulations

Commercial formulations of Doxazosin were successfully analyzed by the proposed methods. The values obtained from the proposed and reference methods were compared statistically by the t and F tests and were found that those proposed methods do not differ significantly from the reported methods and they were presented in Table No.2. The proposed methods also applied for Biological Samples (blood) for recoveries are obtained were recorded in Table No.7.

Accuracy

Recovery studies were carried by applying the method to Drugs sample present in formulations of Doxazosin. (Standard addition method) Similarly the recovery studies were carried by applying the method to Biological sample (blood) to which known amount of Doxazosin correspond to 2 mg formulations taken by the patient. By the following of Standard addition method 2mg of label claim was added. After the addition of these standards the contents were transferred to 100ml volumetric flash and dissolved in solvent. Finally the volume was made up to the mark with solvent. The solution was filtered through Whitman No.41 filter paper. The mixed sample solutions were analyzed and their absorbance value was determined. At each level of recovery five determinations were performed and present in Table No.3. The results obtained were compared with expected results and were statistically validated in Table No.4.

Linearity and Range

The linearity of analytical method is its ability to elicit test results that are directly proportional to the concentration of analyze in the sample within a given range. The range of analytical method is the interval between the upper and lower levels of analyze that have been demonstrated within a suitable level of precision, accuracy and linearity.

Specificity and Selectivity

Specificity is a procedure to detect quantitatively the analyse in the presence of components that may be expected to the present in the sample matrix. While selectivity is a procedure to detect the analyse qualitatively in presence of components that may be expected to present in the sample matrix. The excipient in formulations was spiked in a pre weighed quantity of drugs and then absorbance was measured and calculations were done to determine the quantity of the drugs.

Repeatability

Standard solutions of Doxazosin were prepared and absorbance was measured against the solvent as the blank. The Absorbance of the same concentration solution was measure five times and standard deviation was calculated and presented in Table No.5 and No.9.

Interferences Studies

The effect of wide range of inactive, ingredients usually present in the formulations for the assay of Doxazosin under optimum conditions was investigated. None of them interfered in the proposed methods even when they are present in excess fold than anticipated in formulations.

Solution Stability

The stability of the solutions under study was established by keeping the solution at room temperature for 48 hours. The results indicate no significant change in assay values indicating stability of d rug in the solvent used during analysis. The results are recorded in Table No.6.

Table No.1: Optical characteristics and precision by (1, 10 –PT)

S.No	Parameter	Visible method
1	Color	Orange red
2	Absorption maxima(nm)	510
3	Beer's law limits (µg ml^{-1})	10 to 60
4	Molar absorptivity (l $mol^{-1}cm^{-1}$)	1.0995×10^4
5	Sandell's Sensitivity (µg cm^{-2})	0.04106
6	Regression equation (Y*)	------
7	Slope (b)	0.02194
8	Intercept(a)	0.00662
9	Standard deviation(SD)	0.00405
10	Correlation coefficient (r^2)	0.9997
11	%RSD (Relative standard deviation)*	0.5318
12	Range of errors	------
13	Confidence limits with 0.05 level	0.00324
14	Confidence limits with 0.01 level	0.00425
15	Limits of detection (LOD)(µg ml^{-1})	0.60916
16	Limits of quantification (LOQ) (µg ml^{-1})	1.845

*RSD of six independent determinations.

Table No.2: Assay results of Doxazosin in formulations by UV-Vis method

S.No	Name of the Formulation	Formulation (mg)	Amount found by the proposed method (mg)	Amount found by the reference method[28] (mg)	% Recovery
1	Doxacard	250	249.43 t=0.498* F=0.9998*	244.5	99.77
2	Duracard	250	248.3 t=0.4986* F=0.996*	246.0	99.32

*t and F- values refer to comparison of the proposed method with reference method.

*Theoretical values at 95% confidence limits t= 0.0029 and F= 5.4495

Table No.3: Determination of accuracy of Doxazosin

S.No	Amount of Dox in Formulation (mg)	Amount of Standard Dox added (mg)	Total amount found (mg)	% Recovery
1	248.65	200	447.57	99.46
	247.35	200	445.23	98.94
	247.12	200	444.81	98.85
2	248.32	250	496.64	99.32
	248.3	250	496.6	99.32
	247.9	250	495.8	99.16
3	248.31	300	546.28	99.32
	247.99	300	545.57	99.2
	247.6	300	544.72	99.04

Table No.4: Statistical data for accuracy determination

S.No	Total amount found (mean)	Standard deviation	%RSD
1	445.87	0.825	0.185
2	496.34	0.236	0.0475
3	545.52	0.3555	0.0651

The results are the mean of five readings at each level of recovery.

Table No.5: Repeatability data for Doxazosin at 510 nm

S.No	Conc. ($\mu g\ ml^{-1}$)	Abs 1	Abs2	Abs3	Mean	Std. deviation	(%) RSD*
1	10	0.221	0.22	0.219	0.22	0.001	0.454
2	20	0.433	0.432	0.433	0.432	0.0057	1.319
3	30	0.635	0.634	0.636	0.635	0.001	0.157
4	40	0.878	0.877	0.876	0.877	0.001	0.114
5	50	1.0842	1.083	1.084	1.0837	0.00064	0.055
6	60	1.318	1.317	1.32	1.318	0.00152	0.115

* RSD of six independent determinations.

Table No.6: Stability of the color for 1, 10- phenanthroline method

S.No	Conc. In µg/ml	Time in hours							
1	10	4	8	12	16	20	24	28	32
		0.223	0.223	0.224	0.225	0.225	0.226	0.191	0.115

Table No.7: Assay results of Doxazosin in blood sample

S.No	Name of the formulation	Formulation in (mg)	Amount found by the proposed method in (mg)	Amount found by the reference method[28](A) (mg)	% of Recovery
1	Doxacard	2mg	1.242 t=0.00844* F=0.002979*	1.13	90.08
2	Duracard	2mg	1.225 t=0.00865* F=0.003211*	1.19	97.05

*t and F values refer to comparison of the proposed method with reference method.
*Theoretical values at 95% confidence limits t = 0.00796 and F = 0.0019.

Table No.8: Determination of accuracy of Doxazosin

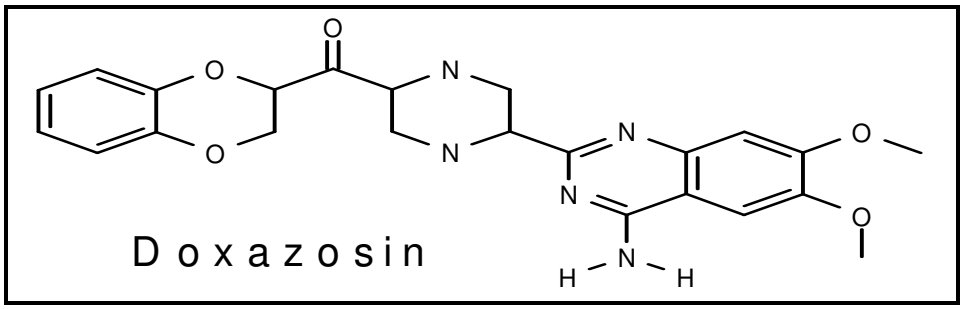
S.No	Name of the formulation in (mg)	Amount of drug in blood sample (mg)	Amount of standard drug added in (mg)	Total amount found (mg)	% Recovery
1	Doxacard (2mg)	1.24	2	3.26	81.5%
2	Duracard (2mg)	1.25	2	3.255	81.37%

The results are the mean of five readings at each level of recovery

Table No.9: Repeatability data for Doxazosin at 510 nm

S.No	Concentration in (µg ml^{-1})	Abs1	Abs2	Abs3	Mean	Std. Deviation	(%) RSD*
1	10	0.0132	0.0133	0.0134	0.0133	0.0001	0.7518
2	20	0.0265	0.0265	0.0267	0.0265	0.0001	0.3773
3	30	0.0398	0.0397	0.0396	0.0397	0.0001	0.2518
4	40	0.0531	0.0531	0.0545	0.0535	0.0008	0.1495
5	50	0.0664	0.0665	0.0667	0.0665	0.000152	0.2255
6	60	0.0797	0.0798	0.0797	0..0797	0.00014	0.1756

* RSD of six independent determinations.



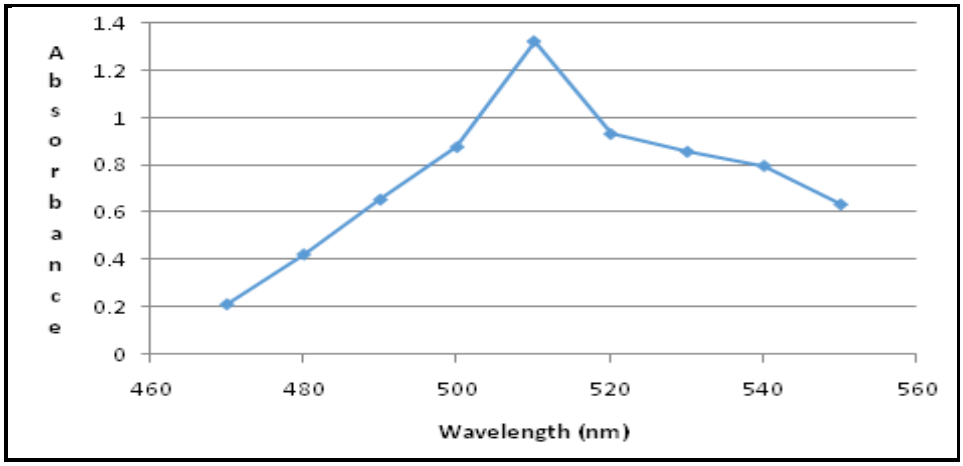


Figure No.1: Absorption spectrum of Doxazosin with 1, 10-Phenanthroline/$FeCl_3$

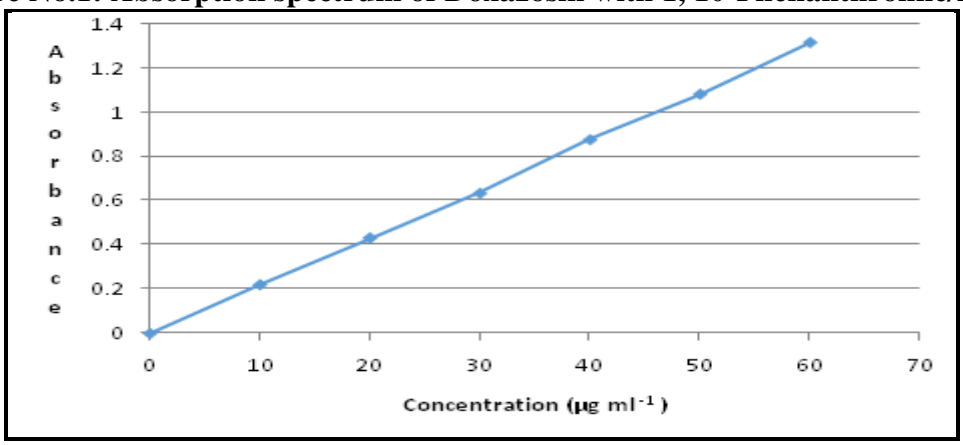


Figure No.2: Beer's law plot of Doxazosin with 1, 10-Phenanthroline/$FeCl_3$

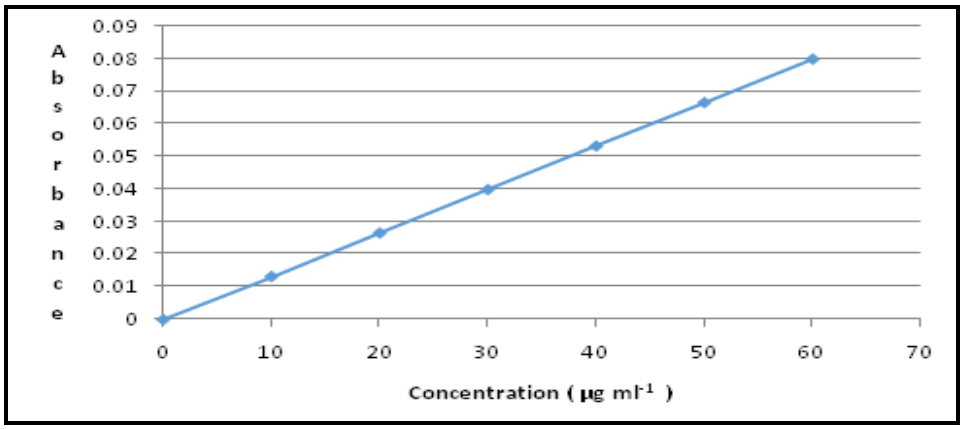


Figure No.3: Beer's law plot for Doxazosin in blood sample

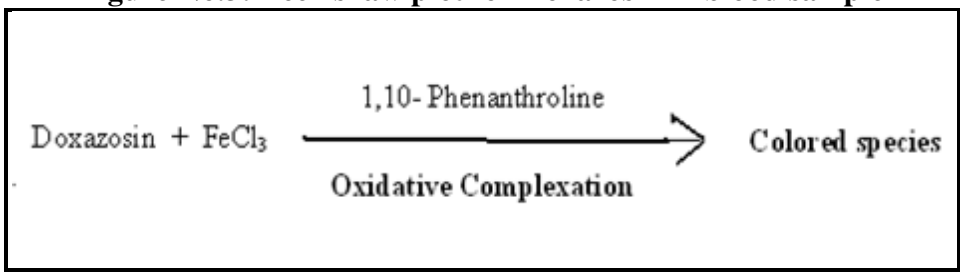


Figure No.4: Chemical reaction of Doxazosin with 1,10 - Phenanthroline

CONCLUSION

The method was found to be accurate and precise, as indicated by recovery studies close to 100 and % RSD is not more than 2. The summery of validation parameters of proposed UV- Vis method is given. The simple, accurate and precise UV- V is method for the determination of Chloramphenicol as bulk, commercial samples and blood samples has been developed. The method may be recommended for routine and quality control analysis of the investigated pure in bulk and samples. The analytical solution is found to be stable up to 48 hrs at room temperature. Hence, it is concluded that the analytical method is validated and can be used for routine analysis and for stability study.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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