Research Article

MICRODETERMINATION OF CARVEDILOL AND ARIPIRAZOLE USING HAEMATOXYLIN DYE IN PURE FORM AND PHARMACEUTICAL FORMULATIONS USING SPECTROPHOTOMETRY

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ABSTRACT

The current study reports about simple, rapid, sensitive and economic spectrophotometric method for determination of the antihypertensive, Carvedilol (CRV) and the antipsychotic, Aripiprazole (ARP) in pure form and pharmaceutical formulations. The suggested method is based on reaction of the studied drugs with haematoxylin reagent in the presence of boric acid to give a reddish violet chromogen at $\lambda_{\text{max}} = 560$ nm. The percentage recoveries for the suggested method were 99.78 ± 1.10 and 99.97 ± 1.2 within the concentration ranges of 3-16 $\mu\text{g/mL}$ and 8-32 $\mu\text{g/mL}$ for Carvedilol and Aripiprazole respectively. Results show a minimum detection limit (LOD) of 0.63 and 1.79 $\mu\text{g/mL}$ and a quantification limit (LOQ) of 1.91 and 5.42 $\mu\text{g/mL}$ for Carvedilol and Aripiprazole respectively. The method showed excellent precision, with intra and inter-assay precisions of less than 2.0% at all concentrations. The suggested method was applied successfully for determination of the cited drugs in pure form and pharmaceutical formulations without interference of common pharmaceutical excipients with the method procedure. The suggested method was proved to be valid by analyzing both pure and pharmaceutical formulations, comparing the results obtained with those of the reported methods and demonstrating good accuracy and precision results.

KEYWORDS: Carvedilol, Aripiprazole, haematoxylin dye, Spectrophotometry, Pharmaceutical formulations

INTRODUCTION

CRV is a beta-adrenoceptor antagonist, indicated for the treatment of hypertension, heart failure and angina pectoris¹. CRV has been assayed in the British pharmacopeia² which introduces a non-aqueous titration method for its estimation. Some spectrophotometric methods have been published for estimation of CRV³⁻⁵. Other methods including spectrofluorimetric determination via derivatization with 7-Chloro-4-nitrobenzofurazone⁶, and non-aqueous titration⁷ have been described. Chromatographic methods have been reported for determination of CRV⁸⁻¹¹. Also an UPLC-MS/MS method for assay of CRV and its active metabolite in human plasma was introduced¹².

ARP is an antipsychotic used in the treatment of schizophrenia and in acute manic associated with bipolar disorder¹. There are several reported methods for the determination of ARP using spectrophotometric techniques in pure form and pharmaceutical dosage forms¹³⁻²². Also there are different chromatographic methods have been published for the analysis of ARP including high performance liquid chromatography²³⁻²⁶, gas-chromatography²⁷ and Liquid chromatography-tandem mass spectrometry (LC-MS/MS)²⁸⁻²⁹.

CRV

ARP

Scheme 1: The chemical structures of CRV and ARP

Haematoxylin was³⁰ the most widely used dye for staining cell nuclei in many histological techniques. Haematoxylin or its oxidized form (haematein) has been widely used for the detection and determination of several metal ions^{31, 32}. Oxidized haematoxylin has been used for the spectrophotometric determination of penicillins and cephalosporins³³, phenylephrine hydrochloride³⁴ and some macrolides³⁵.

The previously published spectrophotometric methods for estimation of methyl dopa and etilefrine hydrochloride suffer from some disadvantages such as complex procedures, time consumption and low sensitivity. In this study, a new sensitive and economic spectrophotometric method has been developed for the determination of the cited drugs in pure form and pharmaceutical formulations that overcome these drawbacks. The mechanism of reaction is that these drugs form charge transfer complexes with the oxidized form of haematoxylin dye, showing absorption band at 560 nm that was used for quantitative determination of the studied drugs.

MATERIALS AND METHODS

Chemicals and Reagents

Haematoxylin dye (Sigma Aldrich Chemicals Co. Ltd, England), freshly prepared daily by dissolving 50 mg in 2 mL of 0.5% boric acid and completing the volume to 50 mL with distilled water. It should be stored in cool place in tightly stoppered dark glass bottle. Boric acid was purchased from El-nasr Co. (Egypt). CRV raw material was obtained from Amoun Pharmaceutical Co. (El-Obour city, Egypt). ARP raw material was obtained from SIGMA pharmaceutical industries (Egypt).

Pharmaceutical Dosage Forms

Carvid ® tablets contain 25 mg CRV per tablet (Multi-Apex Pharma, Badr city, Egypt). Aripiprex® tablets contain 10 mg ARP per tablet (Product of SIGMA pharmaceutical industries for AL-Andalus medical company).

Instrumentation

All of the spectrophotometric measurements were carried out using a Shimadzu UV-1800 with matched 1 cm quartz cells (Japan).

General Procedures

Preparation of Stock and Standard Working Solutions

- a) CRV: Stock solution (0.5 mg/mL) was prepared by dissolving 12.5 mg of CRV in 25 mL of methanol. Standard working solution (0.05 mg/mL) was prepared by taking 1 mL of the stock solution then dilution to 10 mL with distilled water. Working solution of CRV was stable for one week.
- b) ARP: Standard working solution (0.4 mg/mL) was prepared by dissolving 10 mg of ARP in 25mL of acetonitrile. Working solution of ARP was stable for one week.

Construction of Calibration Curves

Different aliquots of working solutions, ranging from 0.3 to 1.6 and 0.1 to 0.4 mL of CRV and ARP, respectively was pipetted into a series of 5 mL volumetric flasks, specified volumes of (0.1%) haematoxylin reagent was added. The contents were heated in water bath at 60 °C for the specified times. 1.0 mL of 0.05 % boric acid was added after cooling, the mixture was diluted to 5 mL with distilled water allowed to stand for 10 min. Absorbances of the colored solutions were measured at 560nm against reagent blank treated similarly (Fig. 1).

Procedure for Dosage Forms

Weigh and finely powder ten tablets. Extract an accurately weighed portion of the powder equivalent to about 25 mg of each drug with methanol for Carvid ® tablets and acetonitrile for Aripiprex® tablets by occasional shaking for 10 minutes. Filter the mixture into 25 mL calibrated flask, wash the residue several times with the same solvent and dilute with distilled water in case of CRV and acetonitrile in case of ARP.

Table 1: Analytical parameters for reaction of carvedilol and aripiprazole with haematoxylin reagent.

Parameter	Carvedilol	Aripiprazole
Conc. of boric acid (%)	0.05 % w/v	0.05 % w/v
Volume of Haematoxylin (mL)	0.2 mL	1 mL
Temperature (C°)	60 °C	60 °C
Time of reaction (min.)	10 min.	40 min.
λ_{max} , nm	560	560
Beer's law limits $\mu\text{g/mL}$	3-16	8-32
Regression equation*		
Intercept	0.0193	0.1587
Slope	0.0576	0.0266
Determination coefficient	0.9997	0.9995

*A = a + b C, where C = concentration of drug in $\mu\text{g/mL}$, A = absorbance, a = intercept, b = slope

Table 2: Results of analysis for determination of carvedilol and aripiprazole using haematoxylin reagent

Parameters	Carvedilol			Aripiprazole		
	Taken $\mu\text{g/mL}$	Found $\mu\text{g/mL}$	Recovery %	Taken $\mu\text{g/mL}$	Found $\mu\text{g/mL}$	Recovery %
	3	2.95	98.21	8	8.09	101.17
	4	3.97	99.26	12	12.12	100.97
	7	6.96	99.38	16	15.73	98.28
	8	8.14	101.71	20	19.75	98.74
	12	12.04	100.36	24	24.15	100.61
	14	14.02	100.16	32	32.00	100.01
	16	15.90	99.36			
Mean			99.78			99.97
S D			1.10			1.20
RSD			1.11			1.20
SE			0.42			0.49
Variance			1.22			1.44
Slope			0.0576			0.0266
LOD $\mu\text{g/mL}$			0.63			1.79
LOQ $\mu\text{g/mL}$			1.91			5.42
Apparent Molar absorptivity $\text{L.Mol}^{-1}.\text{cm}^{-1}$	2.456 $\times 10^4$			1.726 $\times 10^4$		

* Average of three different determinations

Table 3: Inter-day and intra-day results for determination of carvedilol and aripiprazole using haematoxylin reagent

Drug		Added ($\mu\text{g/mL}$)	Found ($\mu\text{g/mL}$)	Recovery% $\pm$ SD	RSD%	ER%
Carvedilol	Intraday	8	8.149	101.859 $\pm$ 1.957	1.921	1.859
		16	15.724	98.275 $\pm$ 1.435	1.460	-1.725
	Interday	8	7.911	98.893 $\pm$ 1.695	1.714	-1.107
		16	15.869	99.179 $\pm$ 1.365	1.377	-0.821
Aripiprazole	Intraday	16	15.724	98.275 $\pm$ 1.435	1.460	-1.725
		12	12.254	102.120 $\pm$ 1.100	1.077	2.120
	Interday	16	15.869	99.179 $\pm$ 1.365	1.377	-0.821
		12	12.091	100.762 $\pm$ 1.577	1.565	0.762

Table 4: Application of standard addition technique for determination of carvedilol and aripiprazole through reaction with haematoxylin reagent

Carvedilol (Carvid®)			Aripiprazole (Aripiprex®)		
Taken ($\mu\text{g/mL}$)	Added ($\mu\text{g/mL}$)	Recovery %*	Taken ($\mu\text{g/mL}$)	Added ($\mu\text{g/mL}$)	Recovery %*
3		98.78	12	4	99.31
	3	99.16		8	98.68
	5	99.98		12	98.12
	9	101.66		16	101.82
	13	98.82		20	99.62
		100.09			
Mean $\pm$ SD	99.91 $\pm$ 1.27		99.67 $\pm$ 1.43		
N	4		5		
S.E	0.634		0.638		
V	1.61		2.04		

*mean of three different experiments

Table 5: statistical analysis of results obtained by the proposed method applied on Aripiprex® tablets and Carvid® tablets compared with reported methods

Parameters	Carvid® tablets	Reference method [4]	Aripiprex® tablets	Reference method [13]
N	4	8	5	6
Mean Recovery	99.91	100.02	99.67	99.71
Variance	1.61	0.64	2.04	1.16
$\pm$ S.D.	1.27	0.80	1.43	1.080
$\pm$ R.S.D.	1.27	0.80	1.43	1.083
$\pm$ S.E.	0.634	0.28	0.638	0.441
Student-t	0.186(2.228) ^a		0.043 (2.262) ^a	
F-test	2.52(4.35) ^b		1.76(5.19) ^b	

a and b are the Theoretical Student t-values and F-ratios at p=0.05.

Fig. 1: Absorption spectra of a) 20 $\mu\text{g/mL}$ ARP and b) 5 $\mu\text{g/mL}$ CRV against c) 0.1 % haematoxylin dye in the presence of 0.05% boric acid.

Fig. 2: Effect of volume of 0.1% Haematoxylin dye on the absorbance of 8 µg/mL CRV and 20 µg/mL ARP.

Fig. 3: Effect of temperature on the reaction between 0.1% Haematoxylin dye with 4 µg/mL CRV and 8 µg/mL ARP.

Fig. 4: Effect of reaction time at 60°C on the color intensity of the reaction between 0.1% Haematoxylin dye with 4 µg/mL CRV and 16 µg/mL ARP.

Fig. 5: Continuous variation plot for CRV and ARP (1×10^{-3} M) with Haematoxylin dye (1×10^{-3} M).

Fig. 6: Calibration curves for determination of CRV and ARP using Haematoxylin reagent.

RESULTS AND DISCUSSION

Haematoxylin is first oxidized to haematein in the solution at the concentration used, then the oxidized haematoxylin in the presence of boric acid produce a reddish-violet charge transfer complexes with CRV and ARP measured at 560 nm. The absorption spectra of the reaction products of the cited drugs showed maximum absorption at 560 nm but with different absorptivities. Figure (1) shows the absorbance spectra of the reaction products. At the selected wave length, 560 nm, both drugs have no absorption and the reagent has small absorbance. Factors affecting the reaction product formation were optimized.

Volume of 0.1% Haematoxylin Reagent

For maximum color intensity, 0.2 and 1 mL of 0.1 % solution of haematoxylin reagent was used for CRV and ARP respectively. It was found that increasing the reagent volume did not affect the color intensity as shown in Fig. 2.

Concentration of Boric Acid

Haematoxylin is oxidized spontaneously and slowly, so stabilization of it is very important. It was found that 2 mL of 0.5 % boric acid per 50 mL of Haematoxylin is optimum for the reagent stability, forming haematoxylin borate. The absorbance readings reach the maximum value within 10 min. After this time,

a continuous increase in the readings of absorbance was observed but with a small rate. So, for quenching the reaction, 1.0 mL of 0.05 % boric acid was added.

Effect of Time and Temperature

The reaction rate was found to increase with increasing temperature with a subsequent increase in the slope of calibration graph. It was observed that, above 60 °C unwanted chemical changes might occur, so 60 °C was chosen as the optimum temperature. Complete color development was attained in water bath of 60 °C after 10 and 40 minutes for CRV and ARP, respectively. Results are shown in Fig 3, 4.

Effect of Diluting Solvent

Many solvents were studied such as water, ethanol, methanol, and acetone. It was found that water is the best diluting solvent as it achieves maximum color stability. Other solvents were found to be unsuitable as the formed colored chromogen cannot be extracted with them.

Stoichiometric Ratio

Continuous variation method was used for determining the molar ratios between the cited drugs and haematoxylin. Results showed that the molar ratio is 1:1 for both drugs (Fig. 5).

Validation of the Proposed Method

Linearity

Calibration curves for determination of the cited drugs were constructed by plotting absorbance against drug concentrations. Figure (6) showed that linear calibration curves were obtained in the range of (3-16 µg/mL), and (8-32 µg/mL) for CRV and ARP, respectively with good correlation coefficients indicating excellent linearity over this ranges. Results were summarized in Table 1.

Detection and Quantitation Limits

The LOD was determined by evaluating the minimum level of the analyte which could be detected while the LOQ was the minimum level of the analyte which could be quantitatively determined with acceptable accuracy and precision. The LOD and LOQ were evaluated using the following equations according to ICH guidelines³⁶:

$$\text{LOD} = 3.3 \frac{\sigma}{S}$$

$$\text{LOQ} = 10 \frac{\sigma}{S}$$

Where, σ = the standard deviation of replicate blank responses and S = the calibration graph slope. Results obtained were listed Table 2.

Accuracy

Accuracy of the measurements of the suggested method was determined using the calibration curves of the cited drugs, where mean percentages of 99.78 and 99.97 for CRV and ARP, respectively were obtained indicating high accuracy of the method. Results are listed in Table 2.

Precision

Intraday precision and inter-day reproducibility were evaluated by calculating relative standard deviations and recoveries of three replicate determinations using two different concentrations of the cited drugs. Results obtained by the suggested method were found to be acceptable. Results are listed in Table 3.

Specificity

The specificity studies revealed that the presence of the additives and common excipients in the tablet dosage forms of the two cited drugs didn't show any kind of impurity interference, since mean recoveries lied in the range of 98.68-101.82 as illustrated in Table 4.

Statistical Analysis of the Pharmaceutical Formulation

Carvid® tablets and Aripiprex® tablets have been successfully analyzed by the suggested method. Results obtained were compared to those obtained by applying comparison methods [4, 13] where Student's t-test and F-test were performed for comparison. Results obtained showed that the calculated t and F values were less than tabulated values at $p = 0.05$, which indicate that there is no significant difference between suggested method and comparison methods relative to precision and accuracy. Results are illustrated in Table 5.

CONCLUSION

This study presented a simple, sensitive and very economic spectrophotometric method for micro determination of CRV and ARP. Spectrophotometry has the advantages of simplicity and acceptable sensitivity over the other techniques. The reagents of the suggested method are cheap and easily available, need no pH

adjustment is required and the procedures do not involve any complex sample preparation. These advantages make it is useful for practical quality control analysis of both drugs in pure form and in pharmaceutical formulations without interference from common additives.

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