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Research Article

Chemometric Determination of Valsartan in The Presence of Its Carboxylic Acid-Induced Triiodide Ion Product by Spectrophotometric Method

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ABSTRACT

A new spectrophotometric method optimized with central composite design (CCD) for quantitative estimation of valsartan (VL) in pharmaceutical preparations was developed. The developed method is based on the oxidation of VL with potassium iodate (KIO_3) to form a carboxylic acid derivative. In the presence of the -COOH group, iodide (KI) is oxidized by iodate, leading to the formation of a yellow-colored triiodide ion with an absorption maximum at 352 nm. The CCD, one of the chemometric methods were applied for the determination of the experimental conditions and then Kinetic studies were used for the stability period. The equilibration time was determined as 10 min. The volumes of 0.05 M KI and 0.003 M KIO_3 were calculated as 1.92 mL (0.0192 M) and 2.96 mL (0.000177 M), respectively, and the temperature was measured as 27°C. The method was linear in the concentration range of 6-34 µg/mL (R2: 0.996). The LOD and LOQ were obtained as 0.81 and 2.46 µg/mL, respectively. The pharmaceutical dosage forms were analyzed with developed method, and the obtained results ranged from 98.3% to 102.9%. The developed method was a simple, rapid and inexpensive method for routine analysis of VL in pharmaceutical dosage form.

Keywords: Central composite design, UV-Vis Spectrophotometry, Valsartan.

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1. INTRODUCTION

Hypertension is a common disease in which the force exerted on the arterial walls by the blood carried from the heart to the body is quite high, and is an important risk factor for cardiovascular diseases. It is managed by maintaining blood pressure above 140/90 mmHg [1]. Angiotensin II (AII) receptor antagonists are the newest class of drugs to be introduced in clinical practice for the treatment of hypertension [2]. Valsartan (VL), is an orally active, potent and specific competitive angiotensin II

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antagonist acting at the ATI receptor, which mediates all known effects of angiotensin II on the cardiovascular system, and it is dilates blood vessels and reduces blood pressure by blocking the action of angiotensin [3]. Since VL is one of the important drugs used in the treatment of hypertension, it is desirable to develop a simple, rapid and reproducible analytical methods for measurement of VL. UV-Visible spectrophotometry one of the most used and most important analytical instruments for most drug quality control analysis, because of its simplicity, speed, versatility, cost-effectiveness, quite high accuracy and precision.

Literature survey reveals that there are UV-Vis spectrophotometric determination of VL in pharmaceuticals. These include direct [4-7] and derivative [8-11] UV measurements, formation of selective ion-pair with acidic dyes, namely, bromophenol blue (BPB) [12, 13] and bromocresol green (BCG) [12], and methyl red [13], the charge transfer complexation reaction between VL as n- electron donor and *p*chloranilic acid (*p*-CA) as π-acceptor [14] and its complexes with calcium(II) and magnesium(II) [15]. Direct spectrophotometric methods have some analytical disadvantages: low sensitivity and low selectivity in ultraviolet region [4-7]. In the literature, a very limited number of methods based on formation of complex have been described for the determination of VL [12-15]. The assay method in our study can be presented as an alternative to existing methods. As far as our knowledge is concerned, no analytical procedure based on the formation of a yellow-colored triiodide ion is reported for the estimation of VL in pharmaceutical preparations Although in other sartan drug groups [16, 17]. There are many specific advantages associated with the kinetic spectrophotometry which is considerably simple and fast method such as high sensitivity, selectivity and low limit of detection. In addition, these advantages, the kinetic study of reaction in our method was executed for avoid the interference of colored and/or turbidity background of samples. In this study, the central composite design (CCD), also called response surface methodology (RSM), was employed for the optimization of the reaction conditions. CCD is a useful method for carrying out a limited number of experiments and save the time and effort by the estimation of the optimum conditions. Thus, the aim of this work was to investigate the validation and application of analytical method based on the oxidation of VL with potassium iodate (KIO_3) to form a carboxylic acid derivative, thus in the presence of –COOH group iodide (KI) is oxidized by iodate resulting in the formation of triiodide ion for estimation of VL, using kinetic spectrophotometry and an experimental design known as CCD.

2. MATERIAL AND METHODS

2.1. Instrumentation and Software

A Thermo Scientific brand, Multiscan GO UV-Visible spectrophotometer (51119300 model) with 1.0 nm bandwidth and connected to lenovo brand computer was used

for all of spectral run. Samples were placed in the Hellma quartz 96 Well microplate for scanning and absorbance measurements. Experimental design was performed Stat-Ease Inc. Design-Expert8.0 (USA).

2.2. Optimization of Maximum Wavelength

Maximum wavelength was carried out with mixture of KI and KIO_3 in the presence of VL. Then, the obtained yellow-colored triiodide ion was scanned from 400-800 nm by UV-Visible Spectrophotometric method.

2.3. Chemicals

VL reference standard was purchased from Sigma-Aldrich (Germany). KI, KIO_3, Dimethylsulfoxide (DMSO) and methanol were of analytical grade and again purchased from Sigma-Aldrich (Germany). Deionized water (EASY Milli-Q grade) was used in the all experimental study. Commercial pharmaceutical dosage forms of VL (Cardopan® and Premium®) were purchased from a Pharmacy in Erzurum/Turkey.

2.4. Preparation of Stock, Calibration and Quality Control Solutions

The stock solution of 2 mg/mL VL was prepared in methanol and was stored at 4°C. The 0.05 M KI solution and 0.003 M KIO_3 solution were freshly prepared in ultrapure water. Calibration solutions (6-34 µg/mL) and QC samples (8, 20 and 30 µg/mL) were obtained daily by dilution of respective stock solution with DMSO. 1.92 mL 0.05 M KI and 2.96 mL 0.003 M KIO_3 were added in the obtained solutions and then the volume was completed with deionized water at 27°C. Prepared respective solutions were taken in quartz microplate and kept for 10 min with shaking. In these solutions absorbance values at 352 nm were measured against the blank reagent. In this study, the method previously developed was used by revising it [16, 17].

2.5. Preparation Pharmaceutical Dosage Form

Ten tablets of each formulation were accurately weighed and crushed to fine powder. The approximately 80 mg VL, that is the amount of 1 tablet, was transferred into the flask and 40 mL of methanol was added. Obtained solutions were dissolved by aid of ultrasonication for 15 min and cooled to room temperature. Then the volume was completed to 50 mL with methanol, and then stock solution diluted at 12 µg/mL concentrations with DMSO and 1.92 mL 0.05 M KI and 2.96 mL 0.003 M KIO_3 were added in the obtained solutions and then the volume was completed with deionized water at 27°C, and the obtained solutions were analyzed at 352 nm as mentioned above.

3. RESULTS AND DISCUSSION

3.1. Optimization of UV-Vis Spectrophotometric Method

A few of Angiotensin II (AII) receptor antagonists, known as sartans, include the methyl group of the butyl side chain: Losartan, Irbesartan and Valsartan. As suggested in the literature, the oxidation reaction of irbesartan and losartan can be

monitored spectrophotometrically [16, 17]. A schematic representation of the reactions is shown in **Fig 1.**

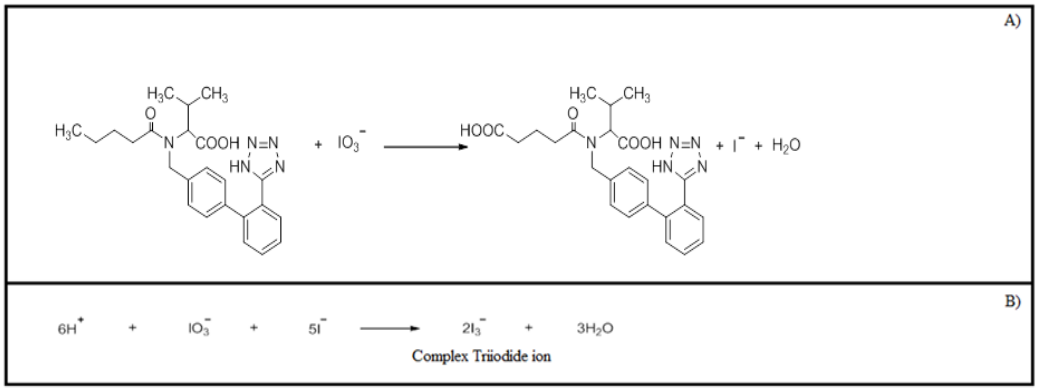

Figure 1. A) The oxidation reaction of VL with KIO_3 to form a carboxylic acid derivative. **B)** The oxidation reaction of KI by KIO_3 in the presence of carboxylic acid form of VL, leading to the formation of a yellow-colored triiodide ion.

Initially, VL was oxidized with iodate and the carboxylic acid form of VL was obtained as a result of this reaction. The production of triiodide ion, which is yellow in color, occurred by oxidation of iodide with iodate in the presence of carboxylic acid form of VL similar to other sartan group drugs found in the literature [16, 17]. The triiodide ion showed the maximum absorbance at 286 nm and 352 nm (**Fig. 2**). The measurements were found to be higher at 352 nm according to the 286 nm as a result of the calculations of molar absorptivity. Therefore, the 352 nm was selected for absorbance measurements in determining of VL.

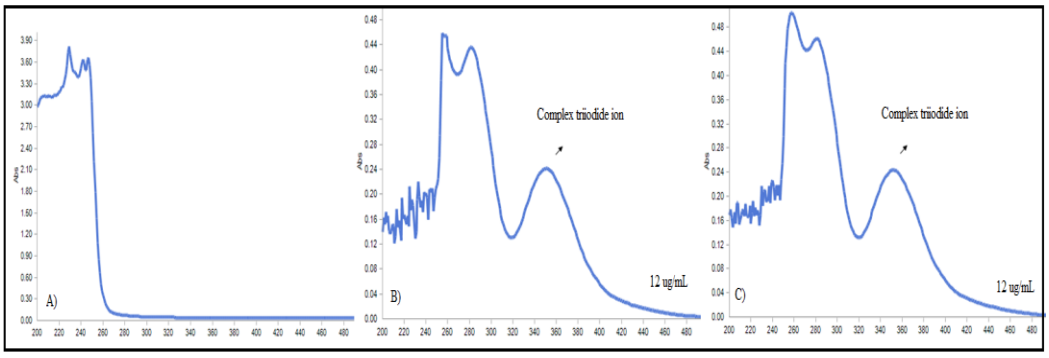

Figure 2. A) Absorption spectra of blank B) Absorption spectra of triiodide complex formed with 12 µg/mL VL standard solution C) Absorption spectra of triiodide complex formed with 12 µg/mL VL drug solution.

Central Composite Design (CCD) is applied in designing the experiments to evaluate the interactive effects of selected factors. For determination of VL, the CCD in three most significant independent factors; 0.05 M KI volume (A), 0.003 M KIO_3 volume (B) and temperature (C) was employed for experimental design and

optimization of results. The choice of these three parameters was realized the result of some preliminary experiments with the help of the prior knowledge of literature [16, 17]. The specified ranges of each parameters were: 0.05 M KI volume (0.6 mL (6.10^{-3} M) - 2 mL (2.10^{-2} M)), 0.003 M KIO_3 volume (0.8 mL ($4.8.10^{-4}$ M) - 2.6 mL ($1.56.10^{-2}$ M)) and temperature (30°C-40°C). The response variables for this experimental design was the absorbance of VL. A set of 20 experiments consisting of 6 axials and 8 factorial runs along with 6 replicates at central point was performed to employ a CCD. The α value was 1.689 ($\alpha = (2^3)^{1/4} \sim 1.689$) as rotational. The absorbance values from each experiment were obtained in the CCD experiments and the three-dimensional RSM plots were made for the estimated absorbances as responses of CCD experiments (**Fig. 3**). The RSM was applied to gain a better understanding of the results and it was concluded that the experimentally obtained actual values were fitted to the response surface. In developing quadratic regression model, the response of tested variables in coded units was given by:

$$Y=0.023A+0.052B-0.00689C-0.040A^2-0.006155B^2-0.012C^2+0,011AB+0.00375AC+0.00125BC+0.25$$

where, Y is the measured response (absorbance). A, B and C are coded values of the above-mentioned independent variables. The statistical significance of the quadratic regression equation demonstrated that the regression is statistically significant with P-value of 0.0455 ($P<0.05$) obtained from the ANOVA for response surface quadratic model. In this case A, B, and C are significant model terms and significantly affects the absorbance of VL. From CCD, the most optimum values of the parameter were found as 0.05 M KI volume: 1.92 mL, 0.003 M KIO_3 volume: 2.96 mL and temperature: 27°C. The predicted absorbance was found as 0.82 with model. Repeated experiments (n=10) were performed by using the optimized conditions to compare the experimentally obtained actual values with the predicted values and the results from ten replications confirmed that the measured mean value was very close to the predicted value with 0.794 ± 0.029.

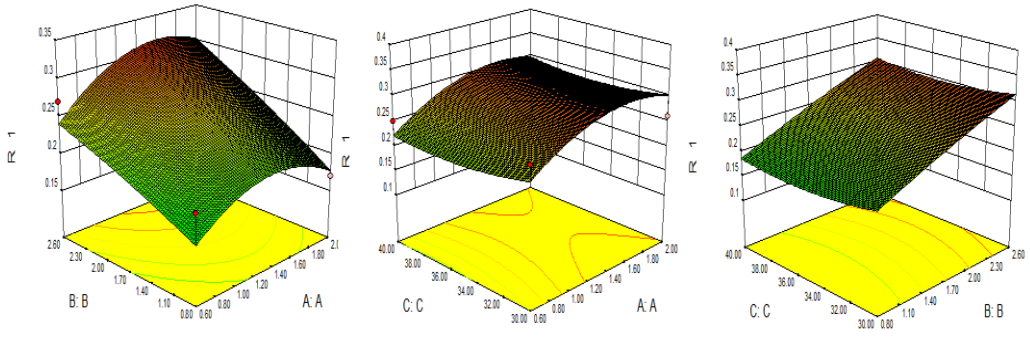

Figure 3. Response-surface plots (Three-dimensional) Y: VL absorbance, X: A) A and B; fixed factor: C, B) A and C; fixed factor: B, C) B and C; fixed factor: A (A:0.05M KI volume, B:0.003M KIO_3 volume, C: Tempereture)

3.2. Kinetic Study

Under the optimized conditions, the absorbance-time curves for the reaction of VL concentration were observed. The calculation of the log IRR (initial reaction rates) as a function of logVL was carried out by utilizing the slope of the curve. According to the data, a straight line whose slope value was found as 1.041 (~1, first order). But the concentrations of KI and KIO_3 concentration were very less than VL. So, the reaction was considered to be a pseudo first order reaction, and triiodide ion formation was determined as the rate-limiting step of the reaction. The reaction time was set as 10 minutes according to absorbance-time curve.

3.3. Validation of UV-Vis Spectrophotometric Method

The new UV-Vis Spectrophotometric method for determination of VL was validated in accordance with ICH Q2B guidance [18].

Linearity was established for the method described above by plotting calibration curves between absorbance and various concentrations of VL (6-34 µg/mL). The mean linear regression equation was calculated based on six calibration curves formed by measuring the absorbance. The related equation was found as A_{286nm}= 0.0335C-0.1722 (C: VL concentration (µg/mL), and A_{286nm}: the absorbance measured at 286 nm) with 0.9996 mean correlation coefficient. The method is linear with very high mean correlation coefficient.

The limit of detection (LOD: 3.3 σ/S) and the limit of quantitation (LOQ: 10 σ/S) were calculated by using the standard deviation of the intercepts (σ) and the slopes (S) of regression lines of the calibration curves. LOD and LOQ obtained from UV-Vis Spectrophotometric method for VL were found as 0.81 µg/mL and 2.46 µg/mL, respectively.

The accuracy and precision of UV-Vis Spectrophotometric method were calculated with intra-day and inter-day measurement for QC concentrations of standard solutions of VL (6, 12 and 24 µg/mL). The results were presented in terms of the percent relative standard deviation (RSD%) for intra-day and inter-day precision of methods and the RSD % values were found to be ≤ 4.28 %. The results were presented in terms of percent relative error (RE%) for intra-day and inter-day accuracy of methods and the RE % values were found to be between -4.11 and 3.25. Recoveries (R%) were carried out by spiking known quantities of standard in pharmaceutical tablets (Cardopan® and Premium®). The obtained results had good accuracy with≤ 99.27 % mean recovery. Also, as we mentioned in our previous study [16], triiodide formation is not affected by pharmaceutical excipients.

3.4. Application of UV-Vis Spectrophotometric Method

The new UV-Vis Spectrophotometric Method was applied the determination of VL in the pharmaceutical dosage forms (Cardopan® and Premium®). Absorption spectra obtained from tablet dosage form (12 µg/mL) was shown in **Figure 2C.** The

estimation of level of VL in the pharmaceutical dosage forms, which was prepared as described in the procedure, was performed and analyses was replicated ten times for the samples. Determinations of VL in pharmaceutical dosage form were successfully achieved with good accuracy results of 98.3%-102.9 % (**Table 1**). The obtained good recovery indicated that the developed UV-Vis Spectrophotometric Method was accuracy enough for the analysis of the drug.

Table 1. Determination of VL in pharmaceutical dosage forms by UV-Vis spectrophotometric method

Drug	Label claim (mg VL per tablet)	Found[a]±SD (mg)	Mean Recovery (%)	RSD (%)	Confidence Interval
Cardopan	80	80.57±2.012	100.72	2.49	98.3-101.5
Premium	80	80.81±1.430	101.01	1.77	99.5-102.9

SD: standard deviation, [a]: Average of twenty-four determinations

4. CONCLUSION

A new UV-Vis spectrophotometric method which is rapid, simple and cheap has been developed with good sensitivity and selectivity. In this study, the CCD was employed as an experimental design for this new analytical method based on oxidation of VL to form triiodide ion. The developed method has an advantage in terms of saving the time and effort by carrying out a limited number of experiments to determine the optimum assay conditions. The kinetic study which is used for determining of the order of reaction and time required for the reaction is another advantage for the method in terms of avoiding the interference of colored and/or turbidity background of samples. The simple reaction conditions were supported with the validation studies. It can be concluded from the results that developed UV-Vis spectrophotometric method is sensitive, specific, accurate and precise. Under the optimum conditions which were selected easily by using CCD, assay results obtained by this method confirmed that the UV-Vis spectrophotometric method is applicable usefully for routine analyses of VL in pharmaceutical dosage forms.

Conflict of Interest

Author has no personal financial or non-financial interests.

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