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Spectrophotometric Investigation of Metal Complexes with Valsartan

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Abstract

To develop a simple, accurate, precision and economical UV-Vis spectrophotometric and mole ratio method for the analysis in pharmaceutical formulations by making its complexes with calcium(II) and magnesium(II). In this study, the separately spectrums of Valsartan and the complexes occured between Ca^{2+} and Mg^{2+} metal ions were taken in ultra-violet area. In addition, stoichiometric ratios of the complexes occured between Valsartan with Ca^{2+} and Mg^{2+} metal ions were determined using mole ratio method. The wavelength of maximum absorption of the spectrum Valsartan and metal complexes with Ca(II) and Mg(II) were determined. The experimental data indicate the formation of metal:ligand = 1:1 complexes for Ca(II)-Valsartan and Mg(II)-Valsartan. Valsartan's recovery rate, it was found in the range of 92.0– 97.5%. Beer's obeyed in the concentration range of 2.18 -10.89 µg/mL for VAL. The LOD and LOQ were found to be 2.21µg/mL and 10.9µg/mL for Valsartan respectively. It is considered that the complexes between Valsartan with Ca^{2+} and Mg^{2+} metal ions would affect treatments positively or negatively.

Keywords: Valsartan, UV-Vis Spectrophotometry, Metal Complex, Mole ratio method, Validation

1. Introduction

Hypertension is the circumstance when the values of diastolic and systolic blood pressure increases above normal values. In other words, hypertension is a cardiovascular disease in which the blood pressure rises above the normal level. According to the etiology of hypertension, two groups are separated as primary and secondary. Primary hypertension accounts for approximately 95% of hypertensive patients but Secondary hypertension constitutes approximately 5% of hypertensive patients [1,2,3]. Antihypertansive drugs are used in the treatment of hypertension. Angiotensin II (A-II) receptor blockers, emerging as a new class of antihypertensive agents, are selective for angiotensin II subtype I (AT1). For instance, Valsartan is an antihypertensive agent and is a member of the class of angiotensin II. Valsartan's chemical name, N-[p-(o-1H-Tetrazol-5-ylphenyl)benzyl]-N-valeryl-L-valine (Figure 1). It is an angiotensin II receptor blocker which inhibits the known activities of type-1 angiotensin II receptor. Thus, it provides to decrease high blood pressure to normal levels which causes narrow blood vessels to enlarge. It is used in heart failure, hypertension (high blood pressure), systolic hypertension, myocardial infraction and left ventricular hypertrophy [4,5,6,7,8,9]. Literature review describes some analytical method for Valsartan. However, there is no study of the stoichiometry of metal complexes formed for this drug with some metal ions. For this reason, the aim of this work is to develop a simple, fast, accurate and precise UV-Vis spectrophotometric method to determine the stoichiometric ratios of complexes formed between Valsartan and some metal ions.

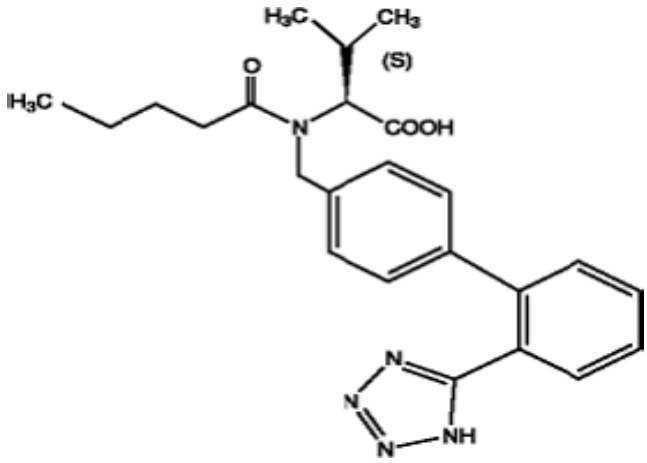

Figure 1. Chemical structure of Valsartan

2. Experimental

2.1. Chemical and reagent

Valsartan was obtained from Sigma-Aldrich Chemical Co. (USA). Calcium nitrate hexahydrate, magnesium nitrate hexahydrate, and methanol reagent were purchased from Merck Chemical (Germany). All the chemicals and solvents were analytical purity.

2.2. Instrument and apparatus

In this research study, the spectrophotometric measurements were carried on out using a Shimadzu UV-2550 UV/Vis double beam Spectrophotometer with 1.0 cm matched quartz cell (Germany). During weighing, Scaltec Sba 31 brand analytical balance were used.

2.3. Preparation of stock standard solutions

2.3.1. Valsartan standard stock solutions

Standard stock solution of $5.0x10^{-3}$ M Valsartan was prepared mixture of methanol and water (50:50, v/v) and transferred into 50 mL volumetric flask to obtain $5.0x10^{-3}$ M of standard stock solution from which desired concentrations of stock solutions were prepared.

2.3.2. Cu^{2+} and Mg^{2+} standard stock solutions

0.0590 g $Ca(NO_3)_2.4H_2O$ weighed and mixture dissolved methanol:water (50:50, v/v) and transferred into 50 mL volumetric flask to obtain $5.0x10^{-3}$ M of standard stock solution from which desired concentrations of stock solutions were prepared. In a similar way, 0.0644 g $Mg(NO_3)_2.6H_2O$ weighed and mixture dissolved methanol:water (50:50, v/v) and transferred into 50 mL volumetric flask to obtain $5.0x10^{-3}$ M of standard stock solution from which desired concentrations of stock solutions were prepared.

3. Method

3.1. Analytical selection of wavelength of Valsartan and metal complexes

In order to select analytical wavelength, working solution of Valsartan was scanned between 400 nm and 190 nm. The overlay spectrum of Valsartan was recorded. The maximum wavelength of Valsartan was determined 249.6 nm (Figure 2).

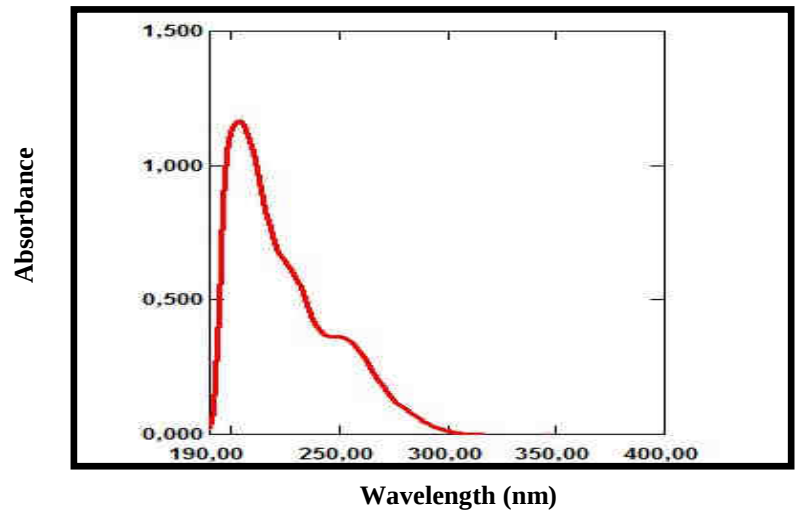

Figure 2. Overlay spectra of Valsartan (2,5x10^{-5} M)

Calcium nitrate tetrahydrate (2.5x10^{-5} M) and Magnesium nitrate hexahydrate (2.5x10^{-5} M) with Valsartan (2,5x10^{-5} M) working solutions were mixed in a separately test tubes respectively. Then, in order to select maximum analytical wavelengths, working solutions of Valsartan-Ca and Valsartan-Mg complexes were scanned between 400 nm and 190 nm and from overlay spectra, the maximum wavelength for both complexes was found 249.6 nm (Figure 3 and 4).

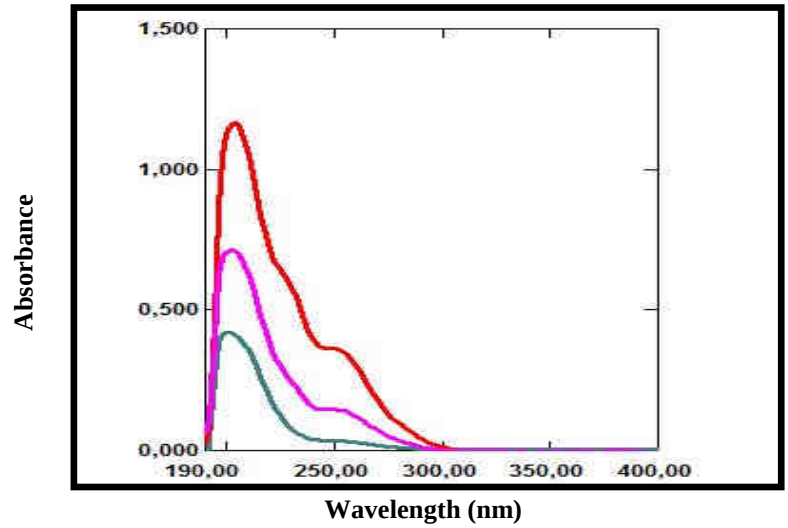

Figure 3. Overlay spectra of Valsartan (2,5x10^{-5} M)

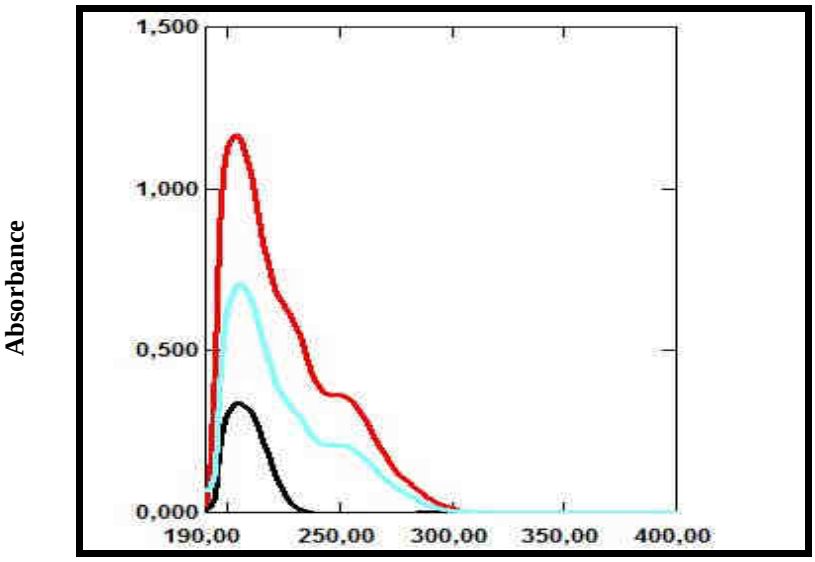

Figure 4. Overlay spectra of Valsartan (2,5x10-5 M)

3.2. Determination of complex stoichiometry

Stoichiometry of the complexes of Ca(II)-VAL and Mg(II)-VAL was determined by using mol ratio method as base. For this purpose, a series of standard solution which the mole ratio of Valsartan and metal ions of Mg^{2+} and Ca^{2+} is between 0-2.5 was prepared in separate test tubes. Then, each solution was mixed in vortex and their absorbances of maximum wavelength were measured on UV spectrophotometer, and a graphic was drawn using the values between ligand:metal mole ratio and absorbance.

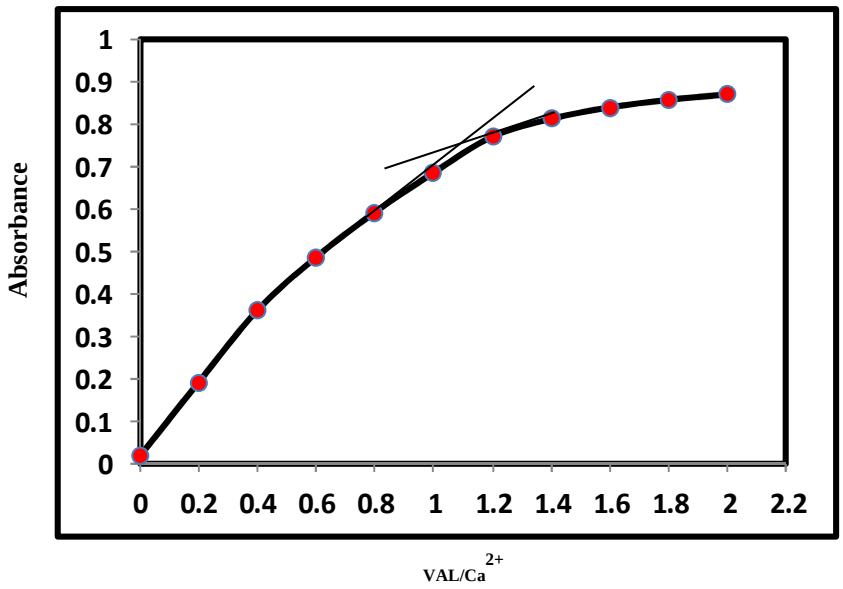

Figure 5. Mole ratio method for Ca(II)-VAL complex

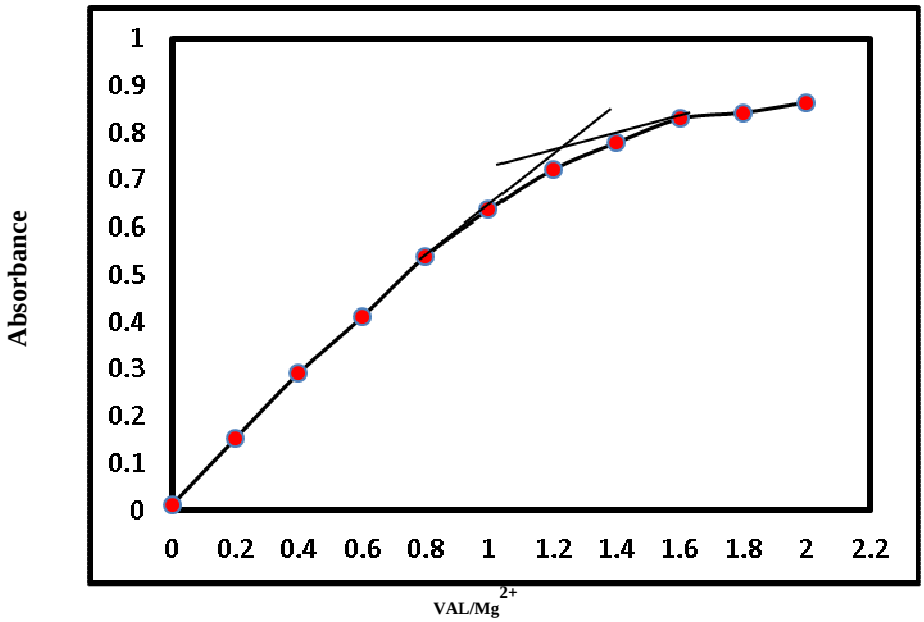

Figure 6. Mole ratio method for Mg(II)-VAL complex

4.Validation

The method was validated interms of accuracy, precision, linearity, LOD and LOQ respectively.

4.1. Linearity and calibration curve

For linearity and calibration curve, working solutions were prepared at 2.18, 4.4, 6.53, 8.7 and 10.89 µg/mL different concentrations respectively The solutions were scanned on spectrophotometer in the UV range 190-400 nm. The absorption spectrum was recorded at 249.6 nm (Figure 7) and a calibration curve was drawn using the values between concentrations and absorbance.

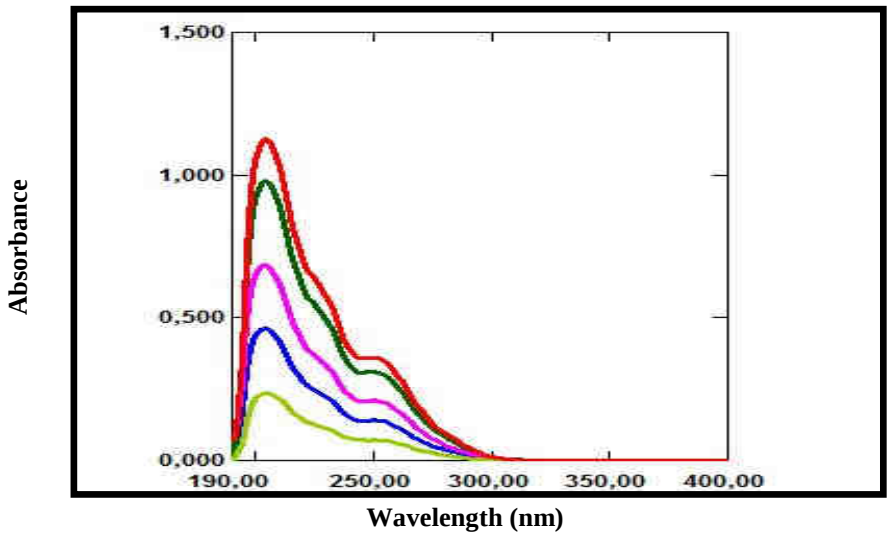

Figure 7. Absorption spectras of five different concentrations (2.18 -10.89 µg/mL) of Valsartan

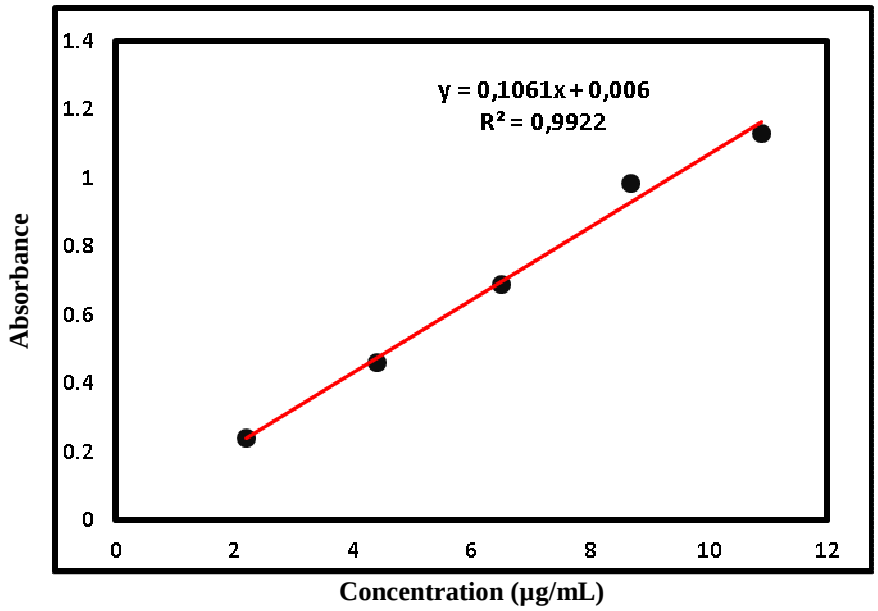

Figure 8. Linearity plot of Valsartan

Table 1. Statistical results of Valsartan's calibration curve

Statistical parameters	Result
Wavelength	204 nm 249.6 nm
Linearity range	2.20-10.89 µg/mL
Regression linear equation	y=0.1061x+0.006
r^2: Correlation coefficient	r^2=0.9922
S_a: Standard deviation on intercept	0.074
S_b: Standard deviation on slope	1.07

4.2. Precision

The precision of analytical method, ıntraday and interday measurements were determined by analyzing different four solutions (3.5, 5.5, 7.5 and 9.5 µg/mL) of VAL within same day and different three days. The average (x), standard deviation (s), percentage relative standard deviation (RSD %) and relative error (BH %) were calculated using the values found.

Table 2. Intra-day and nter-day precision measurements results.

Intra-day measurement values					Inter-day measurement values			
Known value µg/mL	Faound value µg/mL	x̄±s µg/mL	BH %	RSD %	Faound value µg/mL	x̄±s µg/mL	BH %	RSD %
3.5	3.49 3.51 3.52	3.51±0.02	0,29	0.43	3.77 3.78 3.77	3.77±0.01	7.71	0.27
5.5	5.42 5.40 5.39	5.40±0.015	-1,82	0.28	5.38 5.41 5.44	5.41±0.03	-1.64	0.55
7.5	7.32 7.33 7.33	7.33±0.01	-2,27	0.14	7.32 7.33 7.40	7.35±0.04	-2	0.54
8.5	9.28 9.35 9.31	9.31±0.04	-2	0.43	9.14 9.18 9.24	9.19±0.05	-3.26	0.54
x̄: Mean, s: Standard deviation, BH: Relative error, RSD: Relative standard deviation								

4.3. Accuracy

Accuracy of the analytical method was assessed by % recovery studies performed at three different levels, that is, 80%, 100% and 120 %. Calculated amount of Valsartan from stock solution was added in placebo to obtain 80%, 100%, 120% of sample solution. Each sample was prepared in thrice each level. The sample solutions were measured on spectrophotometer in the UV range 190-400 nm. The absorbances of sample solutions were recorded.

Table 3. Recovery studies of Valsartan

	Weighed the amounts of VAL mg/1 tablet	Found the amounts of VAL (mg/1 tabet)	Recovery %
80 %	64	62.4	97.5
100 %	80	77.31	96.64
120 %	96	88.28	92.0
Average recovery			95.38

4.4. LOD and LOQ

Limit of quantification and limit of detection was calculated by the analytical method which based on LOD=C+3s and LOQ=C+10s.

5. Result

The proposed method is based on spectrophotometric and mole ratio method determination of Valsartan with metal complexes UV area using mixture methanol and ultrapure water (50:50, v/v) as solvent. Lambert-Beer's obeyed in the concentration range of 2.18-10.89 µg/mL for VAL (Figure 7). The correlation coefficient value was found 0.9922 which shows that absorbance of the drug was linear with concentration. The visual characteristics such as linearity range, standard deviation on intercept and slope, correlation coefficient and regression linear equation were calculated and are summarized in (Table 1). The percentage recovery was found to be in the range of 92.5-97.5 % for VAL. The result of recovery studies are shown in Table 3. The LOD and LOQ were found to be 2.21 µg/mL and 10.9 µg/mL for Valsartan respectively. The mean, standard deviation, percentage relative error and relative standard deviation were calculated according to the result of ıntra-day and inter-day precision measurements and are summarized in (Table 2). The % RSD values for inter-day analysis was 0.43, 0.28, 0.14 and 0.43 but the % RSD values for intra-day analysis was found 0.27, 0.55 and 0.54 for VAL, respectively (Table 2). As a result, precision of the analytical method was further substantiating. The wavelenghts of maximum absorbtion of the spectrum Valsartan and metal complexes with Ca(II) and Mg(II)

were determined. The experimental data indicate the formation of metal:ligand = 1:1 complexes for Ca(II)-Valsartan and Mg(II)-Valsartan (Figure 5 and 6).

6. Conclusion

In the literature, there is no study on the interaction of Valsartan with calcium(II) and magnesium(II) ions. As a result of the study, literature knowledge on the interaction between Valsartan and metal ions were obtained and we think that the Valsartan metal interaction will contribute to the literature.

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