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Determination of valsartan drug by ion pair complex formation method in tablet form

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ABSTRACT

A rapid, simple, sensitive, spectroscopic, ion pair complex method was developed for valsartan (VAL) in pharmaceutical forms. Resazurin dye was used to form an ion pairing complex with the drug valsartan. analytical characteristics of the proposed method are Beer's law range =10-60 (µg/mL), correlation coefficient (R^2) = 0.9976 , limit of detection (LOD) = 0.1076(µg/mL), limit of quantification (LOQ) = 0.3261 (µg/mL), recovery percentage (%Rec) = (101.9626% - 95.6074%), relative standard deviation (%RSD)= 0.6188% - 0.7148%, Molar absorption (ε)= 4659.85(L/mol.cm), Sandell's index(S) = 0.093458(µg/cm^2),at wavelength 495 nm . The results showed high accuracy and precision of the proposed quantification method for the valsartan drug , and it was of high accuracy and consistent.

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1. INTRODUCTION

Ion pairing describes the (partial) pair of oppositely charged ions in electrolyte solutions to form distinct chemical species called ion pairs. Ion pair formation is invoked as the most plausible explanation either of certain types of direct experimental evidence . If the ion pair is reasonably strong there is usually little difficulty in separating the properties of the ion pair from the long-range nonspecific ion-ion interactions that exist in all electrolyte solutions. However, when the ion pair is weak, there is a strong correlation between these nonspecific ion-ion interactions and ion pair formation . an ion pair, in the context of chemistry, consists of a positive ion and a negative ion temporarily bonded together by the electrostatic force of attraction between them. Ion pairs occur in concentrated solutions of electrolytes (substances that conduct[1]. Ionic pairing is defined as the coupling or combination of ionic species with different charges and their remaining together utilizing Coulomb's force of attraction, without the formation of covalent bonds between them. That is, ionic pairs were formed through electrostatic attraction between charged ions in the solution without the formation of a chemical bond, and Coulomb's law explains the interactions between charged particles[1]. Valsartan drug It is chemically known as N-[p-(o-1H-Tetrazol-5-ylphenyl)benzyl]-N-valeryl-L-valine(4). As shown in Figure 1.

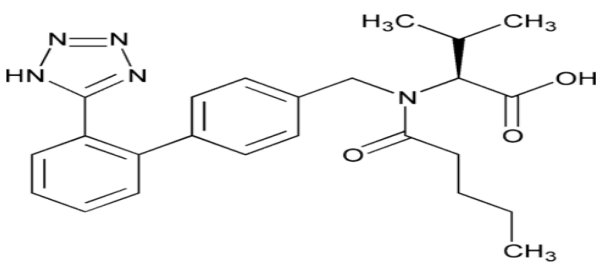

Figure 1. Valsartan drug

A non-peptide drug that lowers blood pressure by inhibiting the action of angiotensin, and its effect is observed two hours after taking it orally [2],[3].Soluble in anhydrous ethanol.Partially soluble in methylene chloride and insoluble in water[4].Valsartan was estimated using several chemical methods, including colorimetric methods [5-7], chromatography[8],[9], and potentiometry[10] . In this research, the ionic pair between resazurin dye and the drug valsartan was carried out, forming a colored complex that was measured spectrophotometrically at a wavelength of 495nm.

2. MATERIALS AND METHOD

practical part :

2.1 Devices used:

The Uv/Vis Spectrophotometer, model SHIMADZU UV-Visible-1650, of Japanese origin, a four-stage sensitive scale, model ADAM BALANCE, of English origin, and the ultrasound device, model ULTRASONIC CLEANER, of Korean origin, were used as well. HANNA acid function measuring device, of Roman origin.

2.1.1 Chemicals used:

The materials used in this method were of high purity and the materials were :

- Ethanol with purity 99.9% of Germany origin, and supplied by SUPELCO Company.
- Hydrochloric acid 37% of Belgium origin, and supplied by CHEM-LAB Company .
- Resazurin with purity 99.8% of England origin, and supplied by BDH Company .
- Sodium hydroxide with purity 97.5% of Indian origin, and supplied by THOMAS BAKER Company .
- Valsartan with purity 100% of Indian origin, and supplied by KOSHER Company .
- Distilled Water .

2.2 Preparation of solutions:

2.2.1 Standard solution of valsartan 100µg/mL:

The standard solution of valsartan was prepared by dissolving 20 mg of it with 80 mL of ethanol, then supplementing the volume with distilled water to 200 mL in a 200 mL volumetric flask.

2.2.2 Resazurine dye solution with a concentration of 100µg/mL:

A solution of resazurine dye was prepared at a concentration of 100µg/mL, by dissolving 20 mg of it in distilled water, and supplementing the volume to 200 mL with the same solvent in a 200 mL volumetric flask.

2.2.3 Hydrochloric acid solution of 0.01M concentration:

This concentration of acid was prepared by withdrawing 0.83mL of 12M hydrochloric acid, and diluting it to 100mL with distilled water in a 100mL volumetric flask, to obtain hydrochloric acid with a concentration of 0.1M, then 1mL of it was withdrawn and diluted to 10mL with distilled water as well.

2.2.4 Sodium hydroxide solution 0.01M:

This concentration was prepared from the base by weighing 0.4g of sodium hydroxide and dissolving it with distilled water, then supplementing the volume to the mark with the same solvent in a 100mL volumetric flask, to obtain a solution of sodium hydroxide with a concentration of 0.1M, then 1mL was withdrawn from it and diluted to 10mL with distilled water as well.

2.2.5 Preparation of buffer solution at pH 5.2:

A buffer solution was prepared at pH 5.2, which consisted of mixing 57.6mL of 0.1M sodium hydroxide and 100mL of 0.1M potassium hydrogen phthalate [11].

2.2.6 Lotevan 160mg pharmaceutical solution at a concentration of 100µg/mL for valsartan:

20 tablets of (LOTEVAN 160mg), produced by Tabuk company (KSA) , were weighed and grinded. The equivalent of the weight of one tablet was 0.5243gm , while the weight of 20 tablets was 10.4860g . containing Valsartan at a concentration of 160mg was put into a 100mL volumetric flask and dissolved with 40mL ethanol and complete the volume to the mark with Distilled water. Valsartan was obtained at a concentration of 100 µg/mL by diluting it with the used solvent consisting of 40% ethanol and 60% water.

3. Results and Discussion

3.1 Initial experiments:

It was observed when mixing 1mL of valsartan with a concentration of (100µg/mL) with 1mL of resazurine dye RZN with a concentration of (100µg/mL) and supplementing the volume to 10mL in a 10mL volumetric flask with the solvent consisting of 40% ethanol and 60% distilled water. It formed a purple complex while the mock solution was blue, so this dye was chosen to form the ion pairing complex with the drug VAL.

3.2 Preparation of Ion Pair for Valsartan:

The valsartan ion pair complex was prepared by mixing 1mL of the drug solution with a concentration of 100µg/ml with 1mL of resazurine dye, also with a concentration of 100µg/ml, in a 10mL volumetric flask, then supplementing the volume to the mark with the solvent consisting of 40% ethanol and 60% distilled water. Spectral scanning of the formed complex was conducted for a range of wavelengths ranging from 200nm to 800nm, where the formed complex gave an absorption at the wavelength of 495nm, while the mock solution gave its highest absorption at the wavelength of 430nm, as shown in Figure 2 .Therefore, this wavelength was fixed in subsequent experiments.

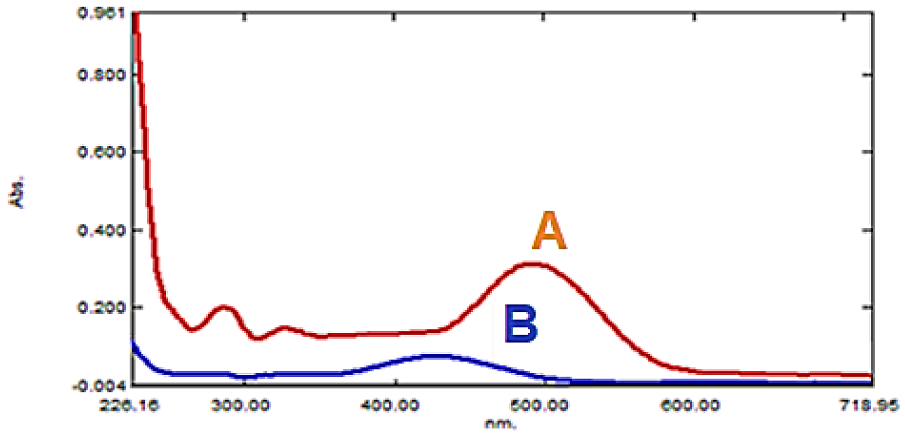

Figure 2. (A) Absorption spectrum of the VAL complex and (B) the blank solution

3.3 Establish the optimum conditions for the method

3.3.1 Choose the type of dye:

Several dyes were tried with the drug valsartan to stabilize the dye that gives the ion pair complex. 1mL of a solution of the valsartan drug at a concentration of 100µg/mL was used with 1mL of each prepared dye at a concentration of 100µg/mL as well, with the volume completed with a solvent consisting of 40% ethanol and 60% distilled water, up to the mark in a 10mL volumetric flask, where alizarin red dye was tried, which did not produce any results, Bromocresol green dye was tried, which formed a complex with the drug. Still , it was unstable, and Bromophenol blue dye, Bromothymol blue dye, Methyl Yellow dye, and Methyl orange, none of which gave any results with the studied drug. When using the resazurine dye, a color change was observed from blue to purple, with constant absorption of the formed complex, and at a maximum wavelength of 495nm for the complex, and 430 $_{nm}$ for the mock solution, so this dye was adopted in the formation of the ion-pair complex, as shown in Table 1.

Table 1. Types of dyes

Sr.No	Dyes	ʎmax	Abs
1	Alizarin red	---	---
2	Bromocresol green	520nm	Unstable
3	Bromophenol blue	---	---
4	Bromothymol blue	---	---
5	Di methyl yellow	---	---
6	Methyl red	---	---
7	Resazurin	495nm	0.1135

3.3.2 The effect of concentration of the dye

To establish the appropriate concentration of resazurine dye (RZN), at which the ion pair complex gives the highest absorption, increasing volumes of the dye were added, ranging from (0.5mL to 5mL), in 10mL volumetric flask containing 1mL of the standard solution of valsartan VAL with a concentration of 100µg/mL then the volume was supplemented to the mark with the solvent used consisting of 40% ethanol and 60% distilled water, where the volume of the dye that gave the highest absorption of the complex formed was fixed, which was 1mL (i.e. concentration 10µg/mL), as shown in Table 2.

Table 2. Effect of dye concentration

Vol. of RZN (mL)	Conc. of RZN µg/mL	Abs.
0.5	5	**0.0925**
1	**10**	0.1136
1.5	15	**0.1095**
2	20	**0.1024**
2.5	25	**0.1014**
3	30	**0.1002**
3.5	35	**0.0874**
4	40	**0.0865**
4.5	45	**0.0862**
5	50	**0.0853**

3.3.3 Effect of Temperature

The effect of temperature on the absorption of the formed complex was studied. The absorption of the complex was measured at different temperatures ranging from 10Cº to 50Cº, where 1mL of VAL drug with a concentration of (100µg/mL) was mixed with 1mL of RZN dye with a concentration of (100µg/mL) in 10mL volumetric flask, and complete the volume to the mark with the solvent used consisting of 40% ethanol and 60% distilled water. It was found that the highest absorption of the complex was at a temperature of 25°C, so this temperature was fixed, as shown in Table 3.

Table 3. Effect of Temperature

Temp.	Abs.
10Cº	0.0954
15Cº	0.1124
20Cº	0.1131
25Cº	0.1138
30Cº	0.1137
35Cº	0.1137
40Cº	0.1134
45Cº	0.1132
50Cº	0.1121

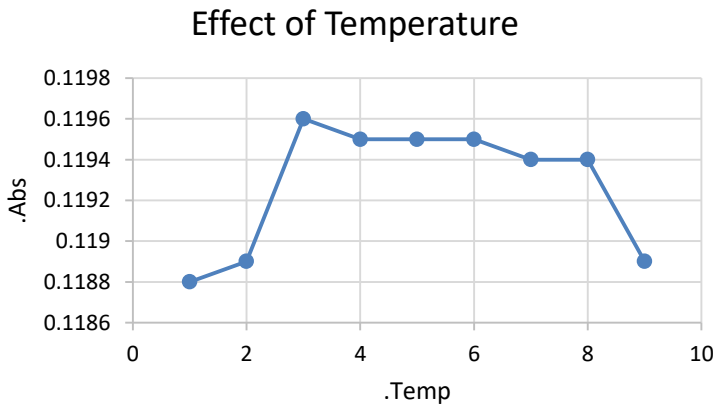

Figure 3. Effect of Temperature

3.3.4 Effect of pH

The effect of changing the acid function on the absorption of the complex formed with the drug VAL was studied. The study was conducted at different values of the acid function, ranging from (3 - 6), where the acid function of the complex formed before adding the acid and base was 5.75, but after adding the acid. An increase in the absorption of the complex was observed, and vice versa with the addition of the base, where a decrease in absorption occurred. The addition of 0.15 mL of hydrochloric acid at a concentration of 0.01M to the formed complex, which had a pH value of 5.2, was confirmed and considered as the best pH, because it gave the highest absorption of the formed complex, as shown in Table 4.

Table 4. Effect of acid function

Addition	Volume in mL	pH	Abs.
HCl [0.01M]	0.05	5.6	0.1152
	0.1	5.35	0.1178
	0.15	5.2	0.1189
	0.2	5.04	0.1182
	0.25	4.85	0.1169
	0.3	4.7	0.1163
---	---	5.75	0.1138
NaOH [0.01M]	0.05	5.92	0.1136
	0.1	6.05	0.1113
	0.15	6.4	0.1089
	0.2	6.62	0.1054
	0.25	6.8	0.1027
	0.3	7.1	0.0985

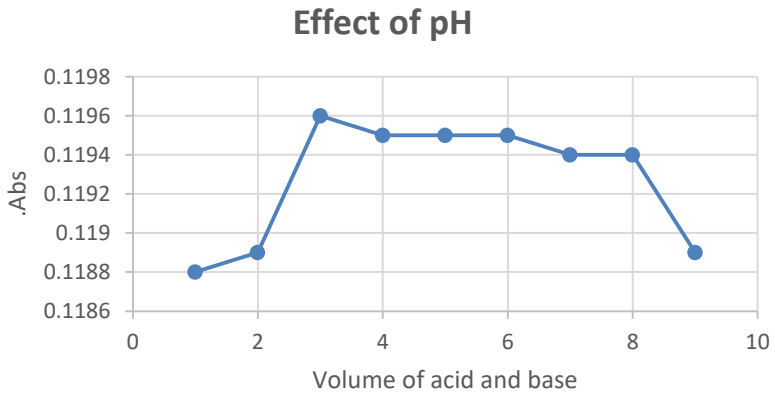

Figure 4. Effect of PH

3.3.5 Effect of Addition Buffer Solution

After stabilizing the acid function 5.2, a buffer solution was prepared at this acid function, which consisted of sodium hydroxide and potassium hydrogen phthalate. Then, increasing volumes ranging from 0.2mL to 1.2mL of the buffer solution were added to a series of 10mL volumetric flask, containing 1mL of VAL drug with a concentration of 100µg/mL, 1mL of RZN dye with a concentration of 100µg/mL, and 0.15mL of hydrochloric acid with a concentration of 0.01M, the absorption was measured at the best conditions proven by the method and at the wavelength 495nm, and it was found that the highest absorption was without adding the buffer solution. Therefore, the effect of adding the buffer solution on the absorption of the ion pair complex was excluded. As shown in Table 5 .

Table 5. Effect of adding buffer solution

Vol. of Buffer Solution in mL	Abs.
With out Buffer	0.1189
0.2	0.1183
0.4	0.1137
0.6	0.1124
0.8	0.1108
1.0	0.1095
1.2	0.1088

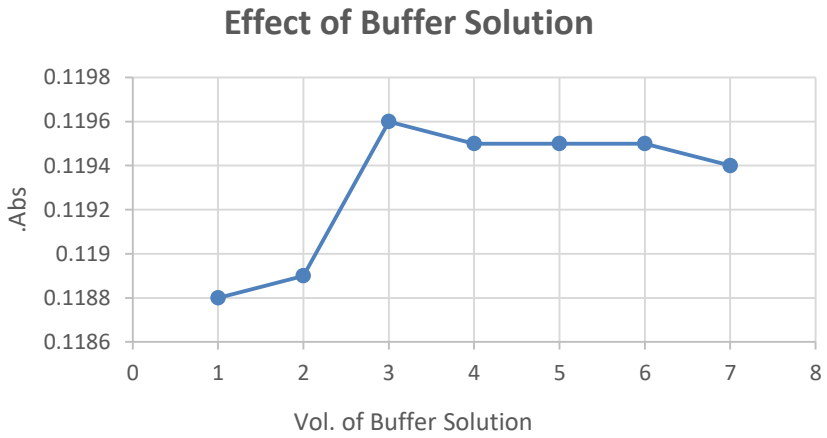

Figure 5.Effect of Addition Buffer Solution

3.3.6 The effect of the sequence of additions

The effect of the sequence of additions to the complex (V), dye (R), and hydrochloric acid (A) on the absorption of the ion pair complex was studied, and as shown in Table 6. listed below, the highest absorption of the ion pair complex was at the sequence Addition of the drug, dye and hydrochloric acid, so this sequence was adopted in the proposed method.

Table 6.Sequence of additions

Sequence of Additions	Abs.
V+R+A	0.1189
V+A+R	0.1187
R+V+A	0.1182
R+A+V	0.1183
A+V+R	0.1178
A+R+V	0.1185

Where :V (the drug), R(Reagent), A (acid)

3.3.7 Effect of Time

The effect of time on the stability and absorption of the formed complex was studied. The study was carried out over a period of different times, ranging from the moment of reaction to 60 minutes, where 1mL of VAL drug with a concentration of (100µg/mL) was mixed with 1mL of RZN dye with a concentration of (100µg/mL) in a 10mL volumetric flask, the volume was completed to the mark with the solvent used consisting of 40% ethanol and 60% distilled water, as the highest absorption of the complex formed was two minutes after its preparation, so this time was fixed in the proposed method, as shown in Table 7.

Table 7. Effect of time

Time (min.)	Abs.
Initial	0.1188
1 min	0.1189
2 min	0.1196
5 min	0.1195
10 min	0.1195
15 min	0.1195
20 min	0.1194
25 min	0.1194
30 min	0.1189
35 min	0.1178
40 min	0.1163
45 min	0.1116
50 min	0.1069
55 min	0.1043
60 min	0.1040

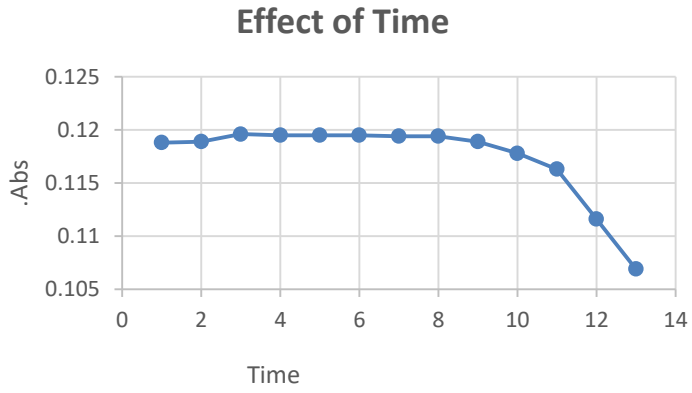

Figure 6. Effect of Time

3.3.8 Calibration Curves of Complex

Increasing concentration of the standard solution of valsartan (100µg/mL) were added into a series of 10mL volumetric flasks, where 1m of resazurine dye (100µg/mL) was added to each volumetric flask, and 0.15mL of Hydrochloric acid with concentration of 0.01M, then the used solvent consisting of 40% ethanol and 60% distilled water was diluted to the mark, and after two minutes had passed, the absorption was measured, and under the best conditions proven by the method, the calibration curve for the drug was drawn, as the linearity of the method was between (10-60) µg/mL, the molar absorption coefficient is 4659.85 L/mole.cm, and the Sandell significance is 0.093458 µg/cm^2, and Figure 7. shows the calibration curve for the drug valsartan.

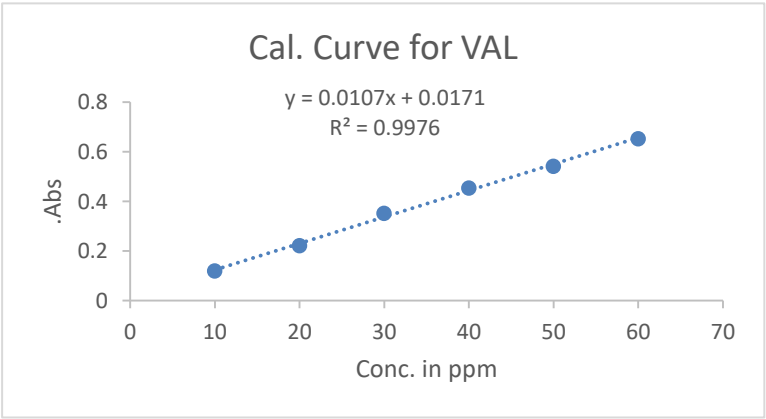

Figure 7. Calibration curve for valsartan

3.4 Job method (Continuous changes)

This method consisted of studying the evolution of the absorbance of solutions with different volume ratios at similar molar concentrations (1×10^{-2}) mol/ml of Valsartan and Resazurin , were added to opposite volumes of Valsartan of (0.9-0.1) ml at 495nm against the test solution, observing that the dye was formed in a ratio of 1:1 (Valsartan:Resazurin), as shown in Figure 8 .

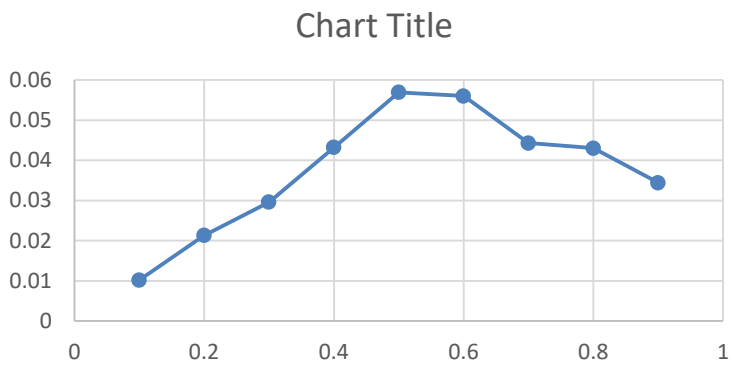

Figure 8. The ratio of the binding between Valsartan and Resazurin

3.5 Accuracy and precision

A study was conducted to calculate the accuracy and compatibility of the proposed method by calculating the percentage recovery value (Rec%) to express the accuracy of the results, and the relative standard deviation coefficient (RSD%) to express the compatibility of the results, for three concentrations of the calibration curve, and by taking six readings for each concentration, where the recovery values percentage ranged between (101.9626% - 95.6074%), and the relative standard deviation values do not exceed (0.7148%), which indicates that the method has good accuracy and agreement, as shown in Table 8.

Table 8. Relative standard deviation and percent recovery values

Conc.taken (µg/mL)	Abs.	Conc.found (µg/mL)	Rec. %	RSD%*
20	0.2217	19.1215	95.6074	0.6188
40	0.4535	40.7850	101.9626	0.6975
60	0.6530	59.4299	99.0498	0.7148

* Replicate analysis (n = 5)

3.6 Limit of Detection and Limit of Quantification

The detection limit and quantitative limit were calculated by measuring the absorption of blanck solutions (because blank solutions are colored), and the calculation was done through the two mathematical relationships [12] . The value of the limit of detection was µg/mL (LOD = 0.1076), and the value of the limit of quantification was µg/mL (LOQ = 0.3261), where the standard deviation of the sample readings was 0.000349 and the slope was 0.0107.

3.7 Apply the proposed method

3.7.1 Direct Method:

Three volumes (2, 4, 6 mL) of the previously prepared drug solution with a concentration of 100µg/mL were withdrawn, placed in three 10mL volumetric flask, and 1mL of the dye solution with a concentration of 100µg/mL was placed, then the volume was completed to the mark with the solvent used. It consists of 40% ethanol and 60% distilled water, to obtain concentrations of (20, 40, 60) µg/mL of valsartan, respectively, according to the best conditions previously established. Calculations were made by conducting six readings for each measurement performed. To express the accuracy of the results, Rec% was used , which was between (100.7788% - 96.2616%), and to express the consistency of the results, RSD% was used, and it did not exceed (0.8653%), which is shown in Table 9.

Table 9.Values of the relative standard deviation and percentage recovery of the drug

Conc.$_{taken}$ in (µg/mL)	Abs.	Conc.$_{found}$ in (µg/mL)	Rec.%	RSD%
20	0.2231	19.2523	96.2616	0.6551
40	0.4418	39.6915	99.2287	0.4217
60	0.6641	60.4672	100.7788	0.8653

3.7.2 Multi Standard Additions Method

(1mL) of the previously prepared drug solution with a concentration of 100µg/mL was added to 7 volumetric flask with a capacity of 10mL. Increasing volumes of the standard VAL solution with a concentration of 100µg/mL (ranging from 1 to 3.5 mL) were added, and the seventh volumetric was left without addition, then a fixed volume of 1mL of the standard solution of the dye was added according to the best established conditions, and the volume was completed with the solvent used consisting of 40% ethanol and 60% distilled water to the mark, after that the concentration of the added solution was plotted against the absorption at the wavelength of 495nm. It is shown in Figure 9.

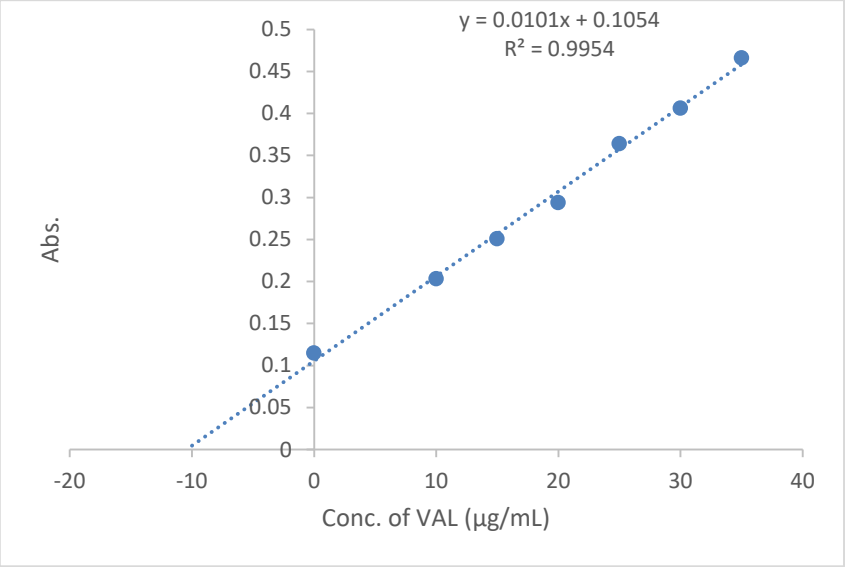

Figure 9. Curve of multiple standard additions

The studied concentration was calculated from the straight line equation shown in the figure above, and the results obtained from applying the multiple standard additives method to the pharmaceutical preparation **Lotevan 160mg**, shown in Table 10, demonstrated the efficiency of the method used in estimation, as Rec% (104.3564) and RSD% (0.3442) were obtained, which indicates that the proposed estimation method is free of interferences.

Table 10. Results of the standard addition method for the VAL complex

Conc.taken (µg/mL)	(Conc.found µg/mL)	Rec %	RSD %
10	10.4364	104.3564	0.3442

4. CONCLUSION

A rapid, simple, sensitive, ion pair complex method was developed for Valsartan (VAL) in pharmaceutical forms. The results showed high accuracy and precision of the proposed quantification method for the Valsartan drug , and it was of high accuracy and consistent . It can be used to estimate valsartan in pharmaceutical preparations

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