EXPLOITING INDIGO CARMINE DYE BLEACHING REACTION FOR SENSITIVE SPECTROPHOTOMETRIC DETERMINATION OF LOSARTAN AND VALSARTAN

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Abstract: *A convenient, precise, and sensitive spectroscopic method was designed for the measurement of losartan (LOS) and Valsartan (VAL) in pure and in pharmaceutical preparations. The technique relies on the oxidation of losartan and Valsartan by adding the oxidizing agent potassium chromate in the existence of sodium oxalate to stimulate the reaction. Then, a quantity of unreacted oxidizing agent is reacted with the indigo carmine (IC) dye in an acidic medium, where a fixed quantity of the dye's blue colour is oxidized to a colorless product at 610 nm wavelength. The technique followed Beer's law for a 1–30 µg/mL concentration range for both losartan and Valsartan, and the molar absorptivity of losartan and Valsartan were (1.959 × 10^4) and (1.524 × 10^4) L/mol.cm., respectively. The limits of detection (LOD) and limits of quantity (LOQ) were 0.0372 and 0.124 µg/mL for losartan and 0.0451 and 0.150 µg/mL for Valsartan respectively, and the technique was successfully applied to pharmaceutical preparations.*
Keywords: *spectrophotometric, Losartan potassium, Valsartan, Indigo Carmine*

Introduction

Losartan potassium is used to treat high blood pressure; it helps lower blood pressure and maintains kidney function. It is also sometimes used to treat heart failure. In cases of overdose, it may cause a significant drop in blood pressure accompanied by a rapid heartbeat. Side effects that may occur in some patients include upper respiratory tract infections, dizziness, and diarrhea, while more serious effects may include severe hypotension or increased sensitivity to light. Therefore, it is advisable to stop using it in women once pregnancy is confirmed to avoid any potential effects on the fetus [1].

The chemical formula for losartan potassium (LOS), a monopotassium salt, is 2-butyl-4-chloro-1-[[2-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol. The molecular weight is 461.01 g/mol. Fig. 1 shows the chemical structure [2].

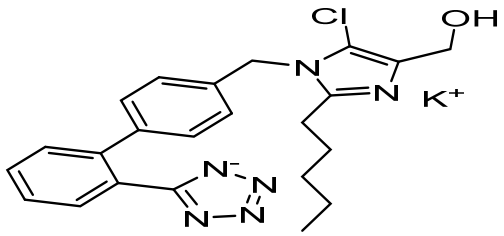


Fig. 1. Structure of Losartan potassium [2]

Losartan potassium can be measured by different methods: spectroscopically [3-7], chromatographically [8-13], and electrochemically [14-15].

Valsartan is commonly used as a medication to treat hypertension, heart failure, and diabetic nephropathy. Usually taken orally, it is the main option for treating high blood pressure. N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine is the chemical representation of valsartan. It has a molecular weight of 435.5 g/mol and the formula $C_{24}H_{26}N_3O_3$, and the chemical structure is shown in Fig. 2 [16].

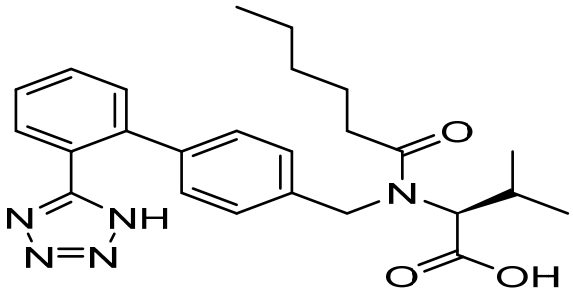


Fig.2. Structure of Valsartan [16]

Several analytical techniques were developed to vary uses of this drug, including spectrophotometry [17-19], chromatography [20-22], and voltammetry [23].

This research used a spectrophotometric method to determine pharmaceutical compounds using a bleaching reaction [24]. The advantage of this proposed determination method lies in its alignment with the principles of green chemistry. It offers simplicity, high sensitivity, and low cost, while completely eliminating the need for heating or harmful solvents. The method's efficiency and versatility have been demonstrated through successful application to the determination of both Losartan and Valsartan under identical experimental conditions, achieving high accuracy and reliability.

Experimental Part

Used Apparatus. The heating operations were carried out using an Electro-mag water bath, while the acidity of the solutions was measured using a Philips PC 700 pH-meter of EUTEC type. An ultrasonic shaker was used to improve the dissolution processes, and measurements were carried out using a Shimadzu UV-1900 Spectrophotometry appliance.

Chemicals Used. High-purity chemicals and analytical reagents were used. Preparation of the solutions of the chemical compounds and drugs is listed in Tables 1 and 2.

Table 1. the chemicals that are ready for the experiments

Chemicals	Concentration	Preparation	Final dilution with water
Losartan potassium	(100μg/mL)	0.0100 g of pure losartan potassium was dissolved in four milliliters of ethanol to create the solution. Warm distilled water was then used to fill the volumetric flask to 100 mL.	100 mL
Valsartan	(100 μg/mL)	0.0100 g of pure losartan potassium was dissolved in 4 mL of ethanol to create the solution. Warm distilled water was then used to fill the volumetric flask to 100 mL.	100 mL
Indigo carmine	(4×10^{-4}M)	The solution was made by dissolving 0.0186g of (IC) dye in distilled water. Then, a volumetric flask was used to fill the volume to 100mL using warm distilled water.	100 mL
Potassium chromate	(1×10^{-3}M)	0.0100 g of pure losartan potassium was dissolved in 4 mL of ethanol to create the solution. Warm distilled water was then used to fill the volumetric flask to 100 mL.	100 mL
Sodium oxalate	(0.1M)	The solution was made by dissolving 1.34 g of sodium oxalate (supplied by Fluka) in hot distilled water. The volume was completed to 100mL in a volumetric flask with distilled water.	100 mL
hydrochloric acid	(1 M)	Hydrochloric acid solution was prepared by diluting 8.29mL of concentrated 12.06 M acid to 100 mL with distilled water using a volumetric flask.	100mL

Table 2. Preparation of drug solution (Losartan potassium-Valsartan) from the pharmaceutical preparation

Tablets Losartan (50-100)mg	Ten tablets of Losartan potassium, each concentration separately (prepared by Pioneer and Micro), were ground, and the average weight of one tablet was taken as 0.01 g, then dissolved in 15 mL of ethanol. The ultrasonic shaker was used for 20 minutes to dissolve the solution completely. Whatman 41 filter paper was used to filter the mixture. 50 mg, or 500 µg/mL, and 100 mg, or 1000 µg/mL, were added to a 100 mL volumetric flask.
Tablets Valsartan (80-160)mg	Weighed 10 tablets of Valsartan preparation, each concentration separately (prepared by Pharma International Co., Amman, Jordan), crushed the tablets, and took the average weight of one tablet equivalent to 0.01 g, dissolved them in 15 mL of ethanol, and used an ultrasonic shaker for twenty minutes to completely dissolve the solution. Whatman 41 filter paper was used to filter the mixture. The concentration of 80 mg was 800 µg/mL, and the concentration of 160 mg was 1600 when the fluid was filled into a 100 mL volumetric flask. By removing 12.5 and 6.25 mL of the two concentrations, respectively, and adding distilled water (100 mL volumetric flask) to fill the volume, a solution with a concentration of 100 µg/mL was created.

Studying the optimal conditions. The optimal conditions for the suggested technique were studied using a 100 µg/mL solution of both potassium losartan and Valsartan (VAL, LOS) in a 10 mL volumetric flask to study the impact of oxidizing agents on the reaction conditions between the compounds under study and (IC) carmine dye.

Discussing the effect of the (IC) dye amount. A 10 mL volumetric flask was filled with 1 mL of hydrochloric acid and various volumes (0.25-2 mL) of indigo carmine dye at a concentration of 4×10^{-1} M. The appropriate amount of distilled water was added. The solutions were left to stand for 5 minutes before measuring the absorbance at 610 nm wavelength, versus a blank solution containing 1 mL of HCl at the same concentration. It was observed that 1 mL of indigo carmine dye gave the best absorbance within a linear relationship; accordingly, it was adopted in the experiments. See the results shown in Figs. 3 and 4.

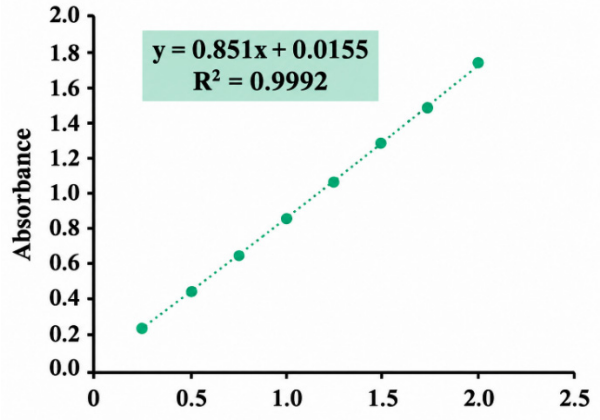


Fig. 3. Standard curve for indigo carmine

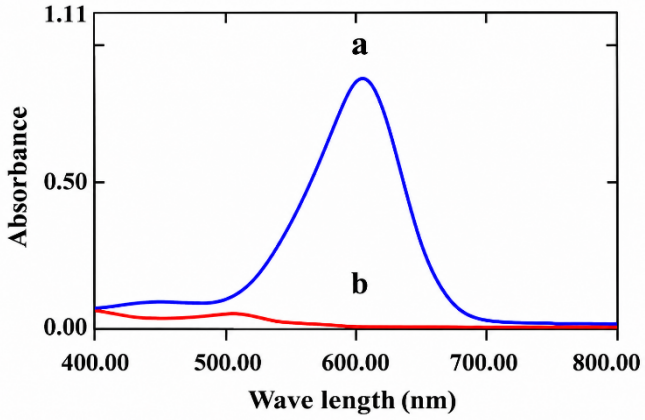


Fig. 4. Absorption spectrum of indigo carmine dye
(a) absorption of indigo carmine dye with hydrochloric acid versus blank solution.
(b) absorption of blank solution containing hydrochloric acid and distilled water versus distilled water.

Investigating the effect of the oxidizing agent type. Various types of oxidizing agents were studied to select the best oxidizing agent for the reaction using 10mL volumetric flask containing 1mL of indigo carmine dye, with (4×10^{-4} M) concentration and 1mL of hydrochloric acid (1M), after

which 1mL of oxidizing agents were added to them, 1.5 mL of sodium oxalate was added to stimulate the reaction (oxalate is a stimulant or activator of the reaction [25]). The potassium chromate and potassium dichromate solutions were left for 2 minutes after the addition of the oxalate. Distilled water was added to fill the volume, and the solutions were allowed to stand for 5 minutes. After that, the absorption was measured at 610 nm wavelength versus the blank solution. Fig. 5 outcomes display that potassium chromate is the most efficient oxidizing agent for bleaching the dye; therefore, it was adopted in all subsequent experiments. The potassium chromate effect size was under study, and the results showed that the optimal
size for bleaching the dye is 0.75 mL.

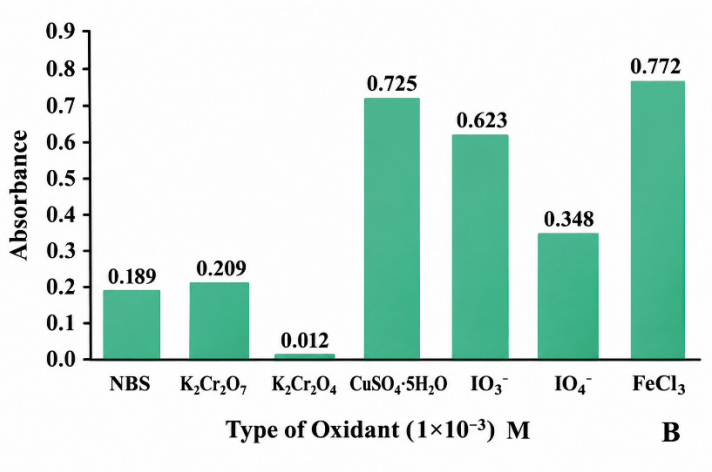


Fig. 5. Effect of the oxidizing agent type on bleaching of the indigo carmine dye.

Effect of acid type and acidity function. Various types of acids at a 1M concentration were studied. Table 3 results indicate that hydrochloric acid is the best for bleaching dyes. It was also shown that using 1 mL volume of hydrochloric acid gave the highest absorbance.

Table 3. Type of acids and pH

Volume mL of acid (1M)	Losartan		Valsartan	
	Absorbance	pH	Absorbance	pH
With out	0.021	6.80	0.030	6.51
HCl	**0.363**	**1.91**	**0.311**	**1.98**
H_2SO_4	0.342	1.81	0.261	2.15
H_3PO_4	0.330	2.00	0.319	2.11
CH_3COOH	0.020	4.91	0.05	4.95

Investigation of the oxalate quantity effect. Different volumes (0-2.5 mL) of $Na_2C_2O_4$, with (0.1 M) concentration, were taken. 1 mL of pharmaceutical compounds (LOS, VAL) was added, and the remaining additions were completed. These solutions were then left for 5 min. after varying quantities of $Na_2C_2O_4$ were added. After adding the dye, the absorbance was measured in comparison to blank solutions. The results are shown in Table 4. Then oxalates play an active role in the oxidation process, as there was no reaction without their addition, and a volume of 1 mL of oxalate solution for (LOS-VAL) gave the best absorption values, so it was chosen in subsequent studies.

Table 4. The effect of the oxalate amount on absorption

mL of 0.1M Oxalate ion Solution	Absorbance	
	Losartan	Valsartan

Without	0.015	0.019
0.25	0.162	0.104
0.5	0.204	0.155
1	**0.416**	**0.319**
1.5	0.363	0.219
2	0.403	0.290
2.5	0.355	0.115

Investigating the oxidation time effect. The results in Table 5 showed that the best time was 10 minutes.

Table 5. Effect of oxidation time

Tim/min	**0**	**3**	**5**	**7**	**10**	**15**	**20**
Absorbance, Losartan	0.98	0.316	0.335	0.394	**0.420**	0.390	0.381
Absorbance, Valsartan	0.009	0.225	0.279	0.309	**0.333**	0.310	0.297

Investigating the surfactant effect. The surfactants were discussed in relation to pharmaceutical compounds (LOS, VAL), and it was found that their impact was negative, thus, they were excluded from subsequent studies.

Effect of Addition Sequence. Various sequences were used in adding the solutions to demonstrate their effect on absorbance, and the results, which are listed, showed that the sequence (D+A+Cr+Ox+IC) used to stabilize the optimal conditions for the reaction gave maximum absorption; thus, it remained in use in subsequent studies.

*D=(LOS, VAL), A=HCl, Cr=$K_2Cr_2O_4$, Ox=Na_2C_2O4, IC=Indigo Carmine

Discussing the impact of time and temperature. The impact of different temperatures (10, 20, and 40°C) was studied under the same conditions established in previous studies. Fig. 6. shows that room temperature (RT=±20°C) achieved the highest absorption values and provided greater stability for at least 60 min.

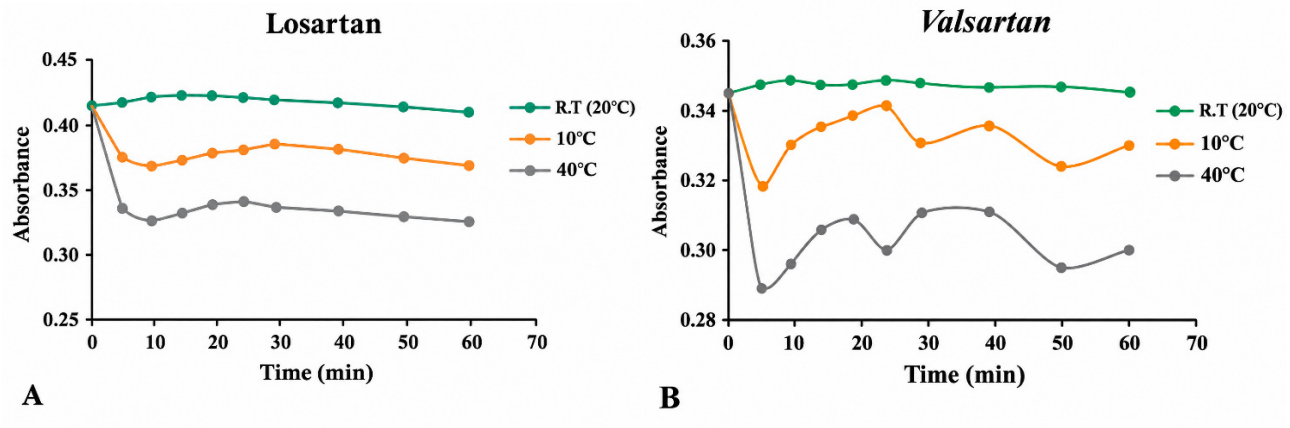


Fig.6. Temperature impact of (A) Losartan and (B) Valsartan

After adjusting the optimal conditions for determining the studied compounds (LOS-VAL), the obtained results are in Table 6.

Table 6. The optimal conditions for determining the (LOS and VAL)

Parameter	**Losartan**	**Valsartan**

(nm)λmax	610	610
Oxidizing agent 1×10^{-3}M	$K_2Cr_2O_4$	$K_2Cr_2O_4$
Volume Oxidizing agent	0.75 mL	0.75mL
HCL(1M)	(1mL)	(1mL)
Volume of 4×10^{-4} M Indigo carmine	0.75mL	0.75mL
Volume of 0.1M Sodium oxalate	1mL	1mL
Temp C°	20°c	20°c
Reaction time(min)	10	10
Development time after dilution (min)	10	5

Final Absorption Spectrum. The final absorption spectrum of the reaction was plotted, after creating the optimal conditions for the studied compounds (LOS, VAL), by taking 1 mL of the pharmaceutical compounds and measuring the absorption at 610 nm wavelength, and the results are illustrated in Fig.7.

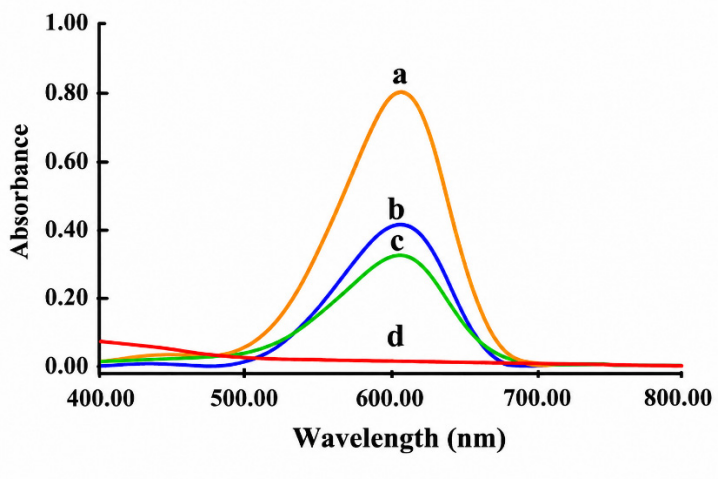


Fig. 7. Final Absorption Spectrum (for losartan potassium and Valsartan):
(a) Absorption spectrum of indigo carmine dye versus blank solution,
(b) 10 µg/mL losartan spectrum in comparison to a blank solution,
(c) Valsartan spectrum at 10 µg/mL compared to blank solution,
(d) Blank solution versus distilled water

Recommended Procedure and Calibration Curve. Following the optimal conditions to determine losartan potassium and Valsartan, the standard curve was prepared according to the following steps: Increasing volumes (0.1-3.0 mL) of losartan potassium and Valsartan at 100 µg/mL concentration were added to two series of 10 mL volumetric flasks, followed by the addition of 1mL of hydrochloric acid at 1 M concentration. Then, add 0.75 mL of $K_2Cr_2O_4$ solution, with (1×10^{-3} M) concentration, 1 mL of oxalate solution with (0.1 M) concentration for potassium losartan and Valsartan. The solutions were left for 10 minutes to complete the oxidation process. Then, the optimal amount of 1 mL of indigo carmine dye solution with (4×10^{-4}) M concentration was added. After adding the dye, the losartan solution was left for 10 minutes, and the Valsartan solution for 5 minutes. The volume was completed to the mark by distilled water. Absorption was measured at 610 nm wavelength. The standard curves are shown in Fig. 8, were obtained to plot the absorbance versus

concentration of the studied pharmaceutical compounds. The method shows that it follows Beer's law in 1-30 µg/mL concentration range for both losartan and Valsartan, as the molar absorptivity value reached (1.959×10^4) and (1.524×10^4) $L \cdot mol^{-1} \cdot cm^{-1}$ for losartan potassium and valsartan, respectively. Table 7 shows the linear specifications of the compounds under discussion. The limits of detection (LOD) and limits of quantity (LOQ) were 0.0372 and 0.124 µg/mL for losartan, and 0.0451 and 0.150 µg/mL for Valsartan, respectively [26].

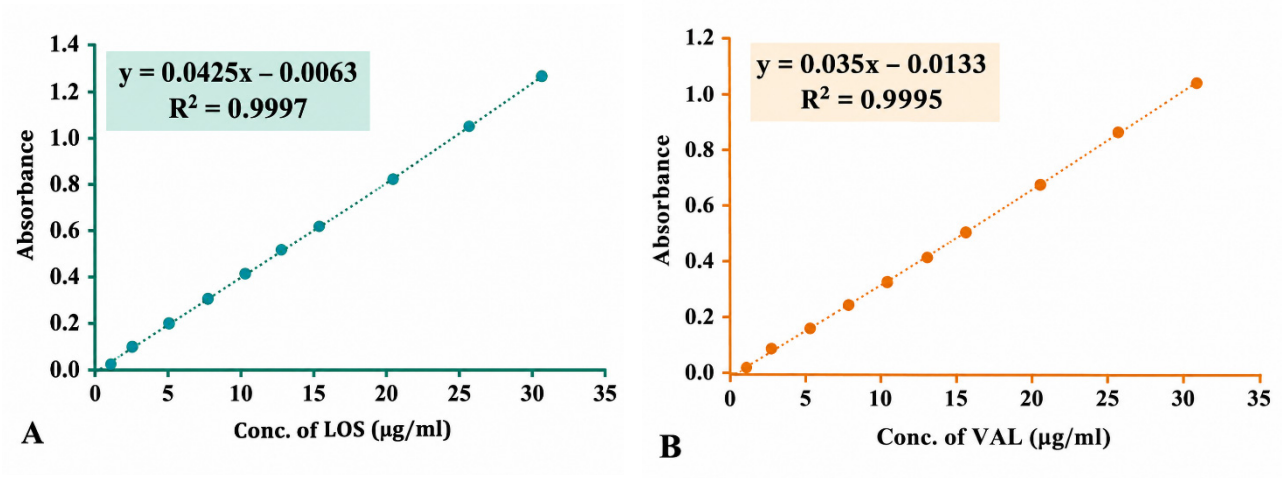


Fig. 8. Standard curves for the pharmaceutical compounds (A) losartan (B) Valsartan

Table 7. Linear specifications of the studied compounds, Losartan and Valsartan

Parameters	Losartan	Valsartan
Linecrity range, (µg/mL)	(1-30)	(1-30)
Molar Absorptivity l/mol.cm)(	1.959×10^4	1.524×10^4
LOD (µg/mL)	0.0372	0.0451
LOQ (µg/mL)	0.124	0.150
Slope	0.0425	0.035
Intercept	0.0063	0.0133
Correlation Coefficient (R^2)	0.9997	0.9995

Precision and Accuracy. Under ideal circumstances, the technique's precision and accuracy were evaluated by calculating the recovery percentage and the relative standard deviation (RSD%) for three distinct concentrations (5, 10, and 20 µg/mL) of both losartan and valsartan (five readings for each). Table 8 results demonstrate this technique's high precision and accuracy.

Table 8. Precision and Accuracy

Drug	Amount Added µg.mL^{-1}		Recovery* %	Average Recovery* %	Relative Error* %	RSD* %	Average RSD %
	Taken	Found					
Losartan	5	4.96	99.2	99.5	-0.8	0.44	0.28
	10	10.09	100.9		0.9	0.21	

	20	19.6	98.4		-2	0.06	
Valsartan	5	5.02	100.4	100.7	0.4	0.55	0.35
	10	10.13	101.3		1.3	0.39	
	20	20.11	100.5		0.55	0.13	

* Average of five measurements

The proposed mechanism for the reaction [27, 28] is illustrated.in Fig.9.

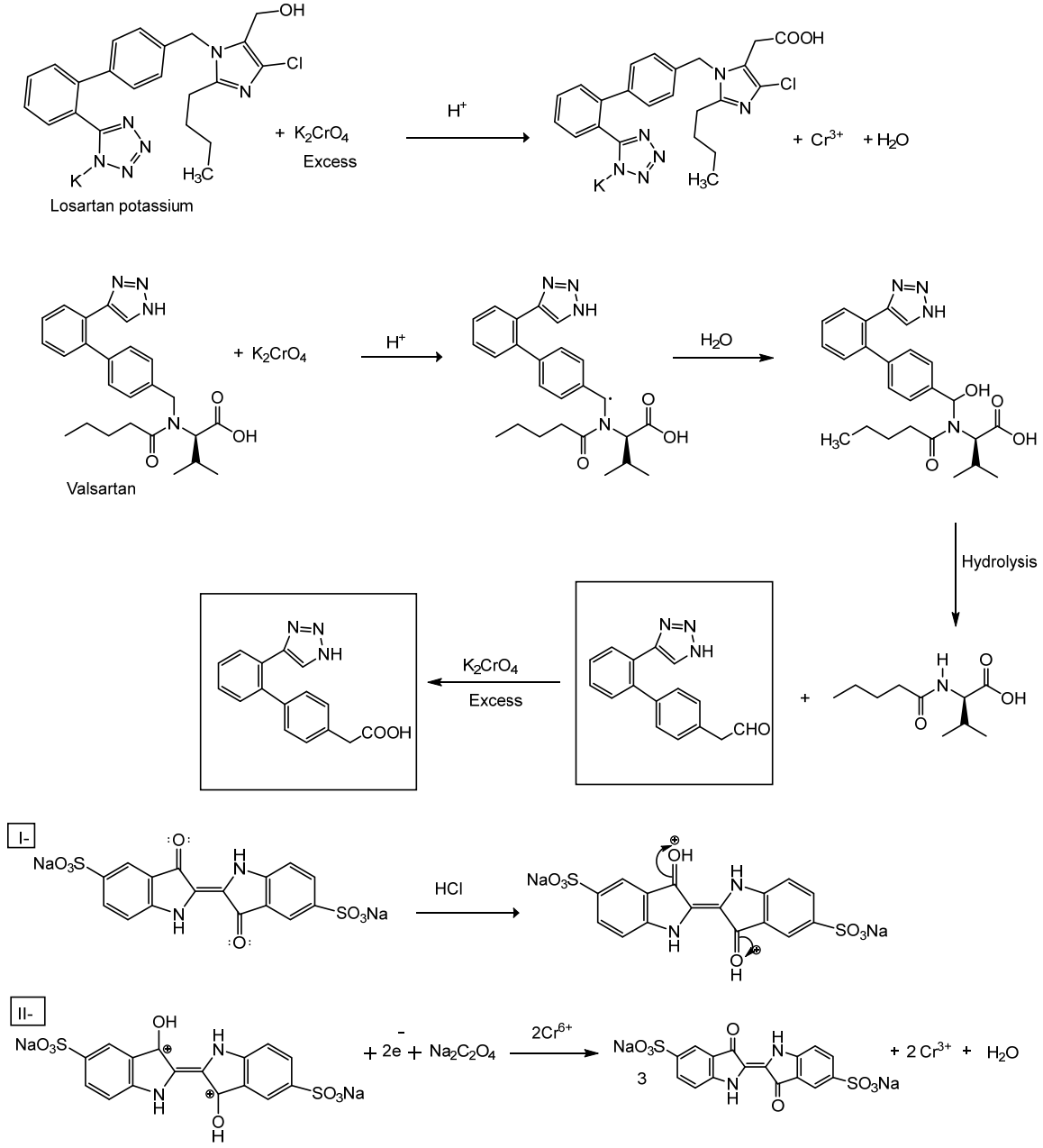


Fig. 9. Proposed mechanism of the reaction [27, 28].

Applying the suggested technique to pharmaceutical preparations. The proposed technique for the determination of Losartan potassium and Valsartan was applied to pharmaceutical preparations in the form of tablets using different concentrations. Table 9. results show that the accuracy is within the range of (0.10-0.94) and the Precision is within the range of (99.1-101.3).

Table 9. Measuring the amount of losartan and Valsartan in pharmaceutical preparations

Drug	Amount Present µg/mL Taken	Recovery* %	Relative Error %	RSD* %	**t-test
Losartan (Tablets), 50mg , Micro	5	100.12	0.12	0.41	0.65
	10	100.4	0.04	0.28	0.31
	20	100.79	0.79	2.03	0.86
Losartan,(Tablets), 100mg (Pioneer)	5	99.52	-0.48	1.39	0.77
	10	99.62	-0.38	0.60	1.422
	20	99.85	-0.15	0.26	1.27
Valsartan, (Tablets) 80 mg, Amman Jorda	5	100.24	0.24	1.31	0.40
	10	99.70	-0.30	0.59	1.14
	20	100.09	0.09	0.34	0.59
Valsartan, (Tablets) 160mg, Amman Jordan	5	99.60	-0.4	1.12	0.80
	10	99.80	-0.20	0.74	0.60
	20	99.94	-0.06	0.34	0.39

*Average of five determinations ; **t-exp: t-experimental, $\pm t = \bar{x} - \mu \times \sqrt{N}/S$, t-value at 95% confidence. level = 2.776

Evaluating the proposed results with the standard addition method. The procedure was used to detect how effective and accurate the proposed technique is in determining losartan and Valsartan, and to confirm their lack of interaction in pharmaceutical preparations. The results are shown in Figs 9 and 10.

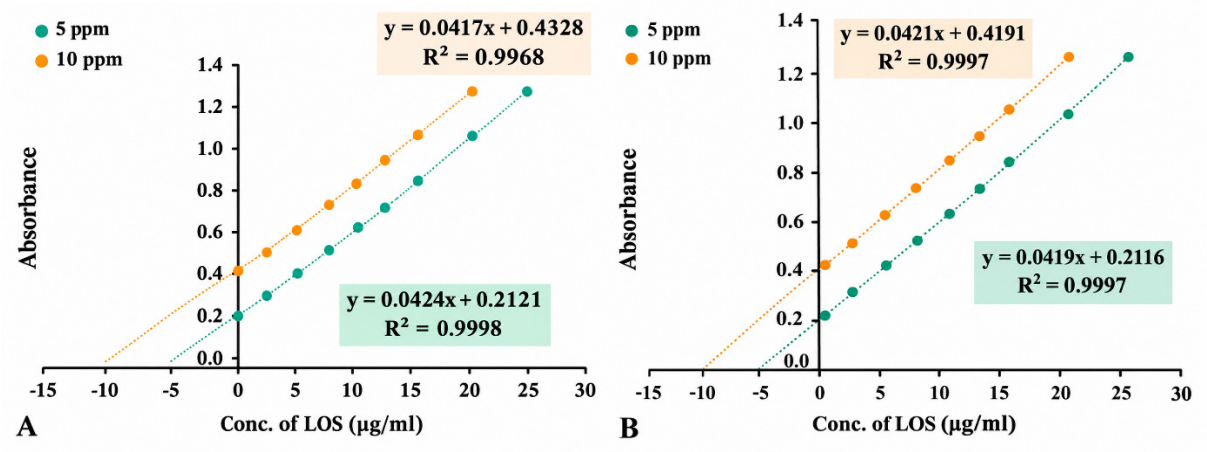


Fig. 10. Losartan A= 50 mg and B= 100 mg

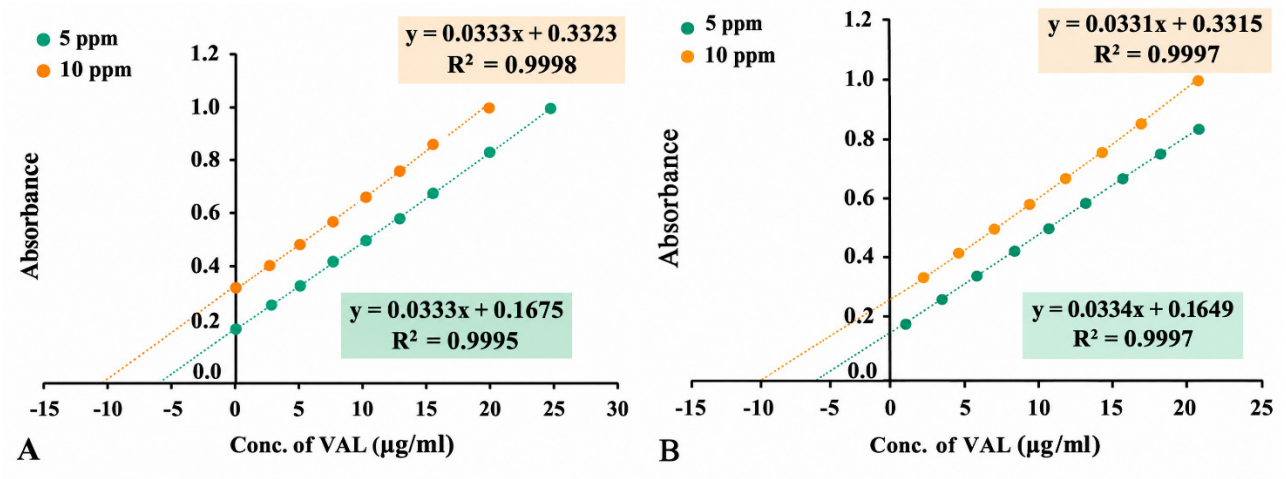


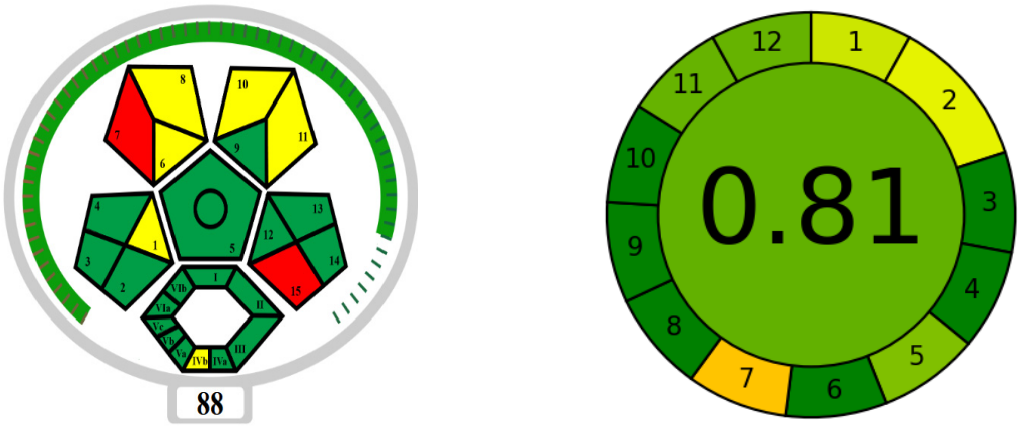
Fig. 11. Valsartan A=80 mg and B=160 mg

Comparison of the proposed method with other spectroscopic methods shown in the Table 10.

Table 10. Method comparison

Analytical parameters	Losartan		Valsartan	
	Present method	**Literature method[29]**	**Present method**	**Literature method[17]**
(nm),λmax	610	520	610	495
Reagent	Indigo Carmine	Erio Chrome black-T	Indigo Carmine	Resazurine
pH	Acidic	Acidic	Acidic	Acidic
Beer's law µg/mL	1-30	25-250	1-30	60-10
Molar Absorptivity l/mol.cm	1.959×10^4	3.0449×10^3	1.524×10^4	4659.85
Recovery,%	99.5	----	100.7	95.6074
RSD,%	0.28	----	0.35	0.6188
R^2	0.9997	0.9998	0.9995	0.9976

Green ness analysis method. The environmental sustainability of the proposed analytical method was evaluated using two complementary greenness assessment tools: the Complex MoGAPI [30] and the Analytical GREEnness Metric (AGREE) [31]. As illustrated in Fig. 12, the proposed method achieved greenness scores of 0.88 and 0.81, respectively, indicating its favorable environmental profile. These high scores highlight the method's compliance with the principles of green analytical chemistry, demonstrating its potential as an environmentally sustainable analytical approach.



A **B**

Fig.12. Evaluation of the greenness of the proposed analytical method using the (A) Complex MoGAPI and (B) AGREE assessment tools

Conclusion

An indirect spectrophotometric method was developed for the sensitive and accurate determination of losartan potassium and valsartan in their pure forms and pharmaceutical formulations. The proposed method is based on the oxidation of the analytes by potassium chromate in an acidic medium, with oxalate serving as a reaction activator. The residual oxidizing agent is subsequently determined through its reaction with a fixed amount of indigo carmine dye, resulting in a decrease in color intensity. The absorbance is measured at 610 nm. Under the optimized experimental conditions, the method exhibited a linear analytical response over a concentration range of 1–30 µg/mL, consistent with the Beer–Lambert law, and demonstrated satisfactory accuracy and precision. The developed method was successfully applied to the quantitative determination of both drugs in commercial tablet formulations.

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