The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM)
ISSN: 2602-3199

The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM), 2019

Volume 7, Pages 236-248

IConTES 2019: International Conference on Technology, Engineering and Science

Electrochemical Behavior of Valsartan, Glimepiride and Their Interaction with Each Other Using Square Wave Voltammetry

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Abstract: In this work an electrochemical quantification and interaction of valsartan and glimepiride were studied on hanging mercury drop electrode (HMDE) using square wave voltammetric (SWV) technique. The effect of temperature on the interaction was investigated in eight degrees of heat and the thermodynamics parameters (enthalpy, entropy & free gibbs energy) were calculated for the interaction using Van't Hoff equation and binding constant (K) also obtained from interaction equation. From the values of the calculated thermodynamic parameters it found that the main bonding forces that predominated over the interaction were Vander Waals and Hydrogen bonding. The calibration curves of each drug was liner with R^2 value equal to 0.9819, 0.997 and the limit of detection was found to be 4.99 x 10^{-7}, 3.48 x 10^{-8} for valsartan and glimepiride respectively. Through the limit of detection, this method can be used as a standard method in estimating the pharmacists in pharmaceutics and verifying the credibility of the manufacturers of the two drugs.

Keywords: Square wave voltammetry (SWV), Valsartan, Glimepiride, Drug interaction

Introduction

Valsartan (VAL) (S)-3-methyl-2-(N-{[2'-(2H -1 ,2 ,3 ,4-tetrazol-5-yl) biphenyl -4-yl] methyl} pentanamido) butanoic acid (Fig. 1), is orally active of antihypertensive drug widely used in the treatment of hypertension (Iriarte *et al.*, 2007), belonging to the family of angiotensin II receptor antagonists acting at the ATI receptor, which mediates all known effects of angiotensin II on the cardiovascular system (Nie *et al.*, 2005).

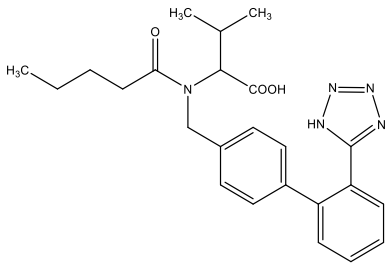

Fig. 1 Valsartan

The methods for the determination of valsartan have been reported in literature including liquid chromatography–tandem mass spectrometry (Koseki *et al.*, 2007), high performance liquid chromatography (HPLC) with a fluorescence detector (FP) (Iriarte *et al.*, 2007 ; Macek *et al.*, 2006), spectrophotometry (Tatar and Saglik, 2002), and there are electrochemical methods (Yan *et al.*, 2008 ; Ramadan *et al.*, 2012 ; Habib *et al.*, 2007).

Glimepiride, 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboximido)ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl)urea, (Fig. 2), is the oral anti diabetic and second –generation sulphonylurea agent. It is

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widely used in the treatment of non-insulin dependent Type II diabetes mellitus (NIDDM) in order to achieve appropriate control of blood glucose level (Davis, 2004 ; Massimo, 2002 ; Campbell, 1998 ; Draeger, 1995 ; Langtry and Balfour, 1998 ; Becic *et al.,* 2003).

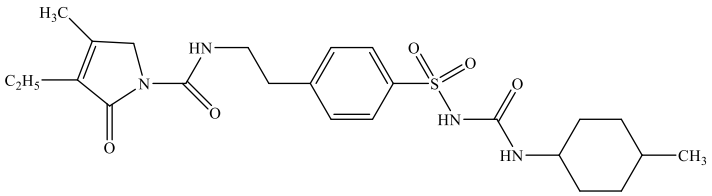

Fig. 2 Glimepiride

Glimepiride have been determination either alone or in combination with various drugs in its pharmaceutical formulations by several methods including high - performance liquid chromatography (HPLC) (Khan *et al.,* 2009), HPLC - tandem mass spectrometry (Wang *et al.,* 2009), high - performance thin layer chromatography (Patel *et al.,* 2006), UV and derivate spectrophotometry (Patel *et al.,* 2006 ; Ravindra and Singhvi, 2008), most of them needs sample preparation or high cost instrumentation.

A drug interaction is a situation in certain medicines can interact pharmacologically and affect the activity of other medicines. This action can be synergistic (when the drug's effect is increased) or antagonistic (when the drug's effect is decreased). These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances (Mohapatra *et al.,* 2018). It is therefore easy to see the importance of these pharmacological interactions in the practice of medicine, if a patient is taking two drugs and one of them increases the effect of the other it is possible that an overdose may occur. The interaction of the two drugs may also increase the risk that side effects will occur. On the other hand, if the action of a drug is reduced it may cease to have any therapeutic use because of under dosage (Alfonso and Gayo, 2005).

an electrochemical behaviour of valsartan and glimepiride were investigated In this work also their interaction with each other was examined for this purpose a simple, sensitive and rapid square-wave voltammetric (SWV) technique was developed. The developed method was applied to determine the valsartan and glimepiride in pharmaceutical formulations. The results obtained were compared with UV- spectrophotometric method given in the literature (Altinoz and Tekeli, 2001).

Experimental

Apparatus

SWV measurements were performed using a 797 VA Computrace connected to a computer unit supplied by Metrohm, Switzerland, coupled with a three-electrodes detection system consists of hanging mercury drop electrode (HMDE) as working electrode, an Ag/AgCl/sat. KCl as reference electrode and 1mm platinum wire was used as an auxiliary electrode.

pH measurements for prepare phosphate buffer solutions were performed using a digital pH meter supplied by HANNA company, Portugal, model pH211, microprocessor pH meter with accurate to ±0.05.
HAAKE G supplied by HAAKE company, Germany, water bath was used for controlling temperature during the measurements.

Reagents and procedure

All chemicals used were analytical grade (BDH , Fluka). The pure valsartan & glimepiride were kindly supplied by Sammira drugs industry in Iraq. Stock solution of each drugs were prepared by using an appropriate amount of valsartan and glimepiride and dissolving it in ethanol absolute and dimethyl formamide (DMF) respectively. The phosphate buffer (K_2HPO_4 & KH_2PO_4) used as supporting electrolyte.

The buffer solution was placed in polarographic cell and deoxygenated via purging with N2 gas for 5min prior the measurements, after recording the buffer voltammogram, the test solution added to the polarographic cell

and the square wave voltammograms were recorded under the optimum conditions for a sequence additions of standard stock solutions of each drugs, then the calibration curves were constructed for each drugs.

Results and Discussion

Electrochemical behavior of valsartan

Square wave voltammograms of valsartan shows a well-defined reduction peak at (-1.07)V on HMDE versus Ag/AgCl/sat.KCl under the default conditions of instrument in phosphate buffer solution (pH=7).

Optimum condition for valsartan

The square wave voltammograms were recorded for 4.97×10^{-5}M valsartan in phosphate buffer at different pHs, of phosphate buffer solution. It can be seen from figure 3, the reduction peak current, peak shape and peak potential depended strongly on pH. The optimum pH was found to be pH=6, which is used for determination, where as pH=7 (human blood pH) was used for interaction studies.

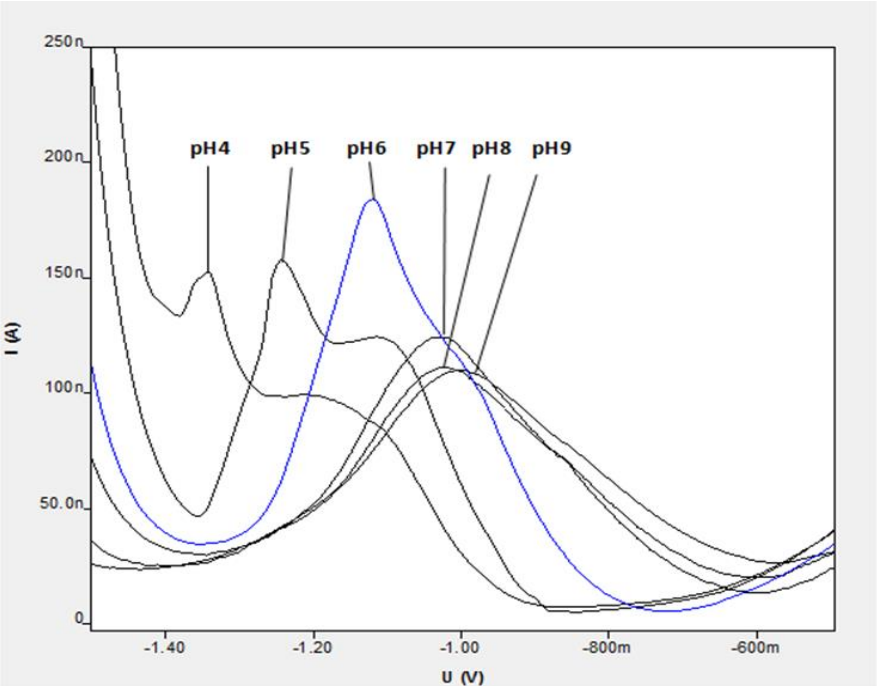

Fig. 3 Effect of pH on the reduction peak current of valsartan

In order to optimize the conditions for measurements, various instrumental and experimental variables such as frequency, scan increment, pulse amplitude, supporting electrolyte and pH were examined and optimized, using 4.97×10^{-5}M valsartan in phosphate buffer as supporting electrolyte, the results obtained are shown in table 1.

Table 1 The optimum condition for valsartan in phosphate buffer solution (pH=6)

Start Potential	-1.5 (V)
End Potential	-0.7 (V)
Deposition potential	-0.6 (V)
Deposition time	30 (s)
Equilibration time	1 (s)
Voltage step	0.006 (V)
Amplitude	0.06 (V)
Frequency	50 (Hz)
Drop size	4
Sweep rate	0.3

Stability of reduction peak

To study the stability of reduction peak of valsartan a voltammogram of 9×10^{-5}M valsartan was recorded under the mentioned optimum conditions (Table 1) versus time, the results obtained are shown in table 2, it is clear that the reduction peak current is stable within the time studied.

Table 2 Stability of reduction peak current ofvalsartan

Time (min)	Ip of VAL (nA)	Ep of VAL (V)
0	284	-1.08
5	287	-1.08
10	278	-1.08
15	278	-1.08
20	291	-1.08
25	291	-1.08
30	296	-1.08
35	276	-1.08
40	275	-1.08
45	278	-1.08
50	277	-1.08
55	279	-1.08
60	280	-1.08

Calibration curve of valsartan

The calibration curve was constructed by adding a sequence addition of standard valsartan solution (10^{-3}M) and the voltammogram was recorded for each addition (Fig. 4) under the previous optimum conditions (Table 1), the plot of peak current versus concentration (Fig. 5) gives a straight line with R^2= 0.9819 concentration range [$(4.99\times10^{-7}$M) – $(6.95\times10^{-6}$M)].

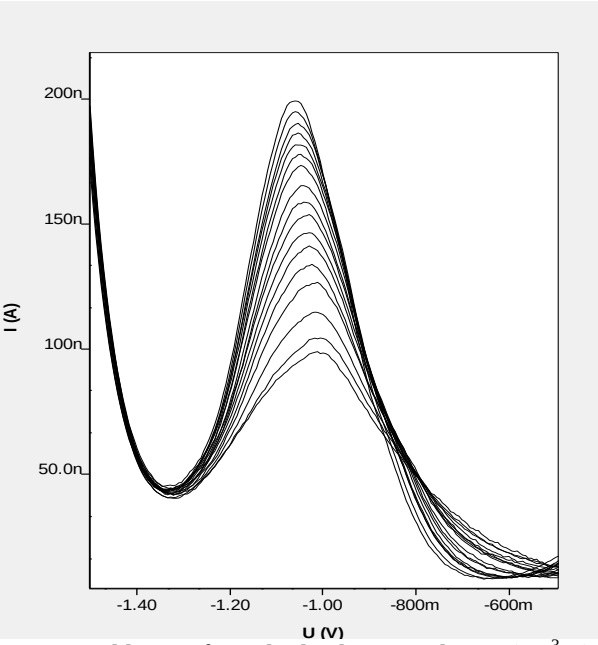

Fig. 4 Voltammograms of sequence addition of standard valsartan solution (10^{-3}M) in phosphate buffer (pH=6)

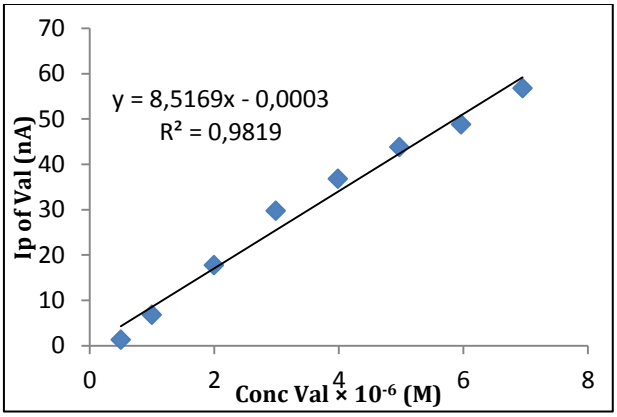

Fig. 5 The calibration curve of valsartan using phosphate buffer (pH=6)

Electrochemical behavior of glimepiride

SWV of glimepiride show a well-defined reduction peak at (-1.3)V versus Ag/Agcl/sat.KCl under the default conditions of instrument in phosphate buffer (pH=7).

Optimum condition for glimepiride

The square wave voltammograms were recorded for 4.97×10^{-5}M glimepiride in phosphate buffer solution at different pHs, It can be seen from figure 6, the reduction peak current, peak shape and peak potential depend strongly on pH. the optimum pH was found to be pH=7.

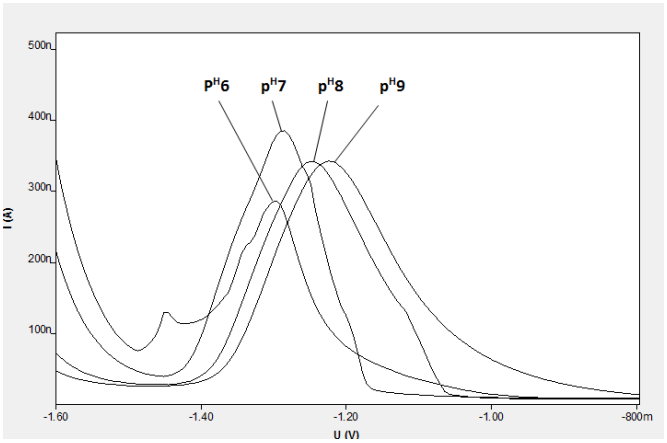

Fig. 6 Effect of pH on the reduction peak current of glimepiride

In order to optimize the conditions for measurements, various instrumental and experimental variables such as frequency, scan increment, pulse amplitude, supporting electrolyte and pH were examined and optimized, using 9.9×10^{-5}M glimepiride in phosphate buffer solution as supporting electrolyte, the results obtained are shown in table 3.

Table 3 The optimum condition for glimepiride in phosphate buffer (pH=7)

Start Potential	-1.6 (V)
End Potential	-0.8 (V)
Deposition potential	-0.8 (V)
Deposition time	70 (s)
Equilibration time	5 (s)
Voltage step	0.006 (V)
Amplitude	0.06 (V)
Frequency	50 (Hz)
Drop size	4
Sweep rate	0.3

Stability of reduction peak

To study the stability of reduction peak of glimepiride a voltammogram of 1.4×10^{-5}M glimepiride was recorded under the mentioned optimum conditions (Table 3) versus time, the results obtained are shown in table 4, it is clear that the reduction peak current is stable within the time studied.

Table 4 Stability of reduction peak of glimepiride

Time (min)	Current (nA)
0	155
5	154
10	155
15	155
20	155
25	154
30	153
35	152
40	152
45	151
50	151

The calibration curve of glimepiride

The calibration curve was constructed by adding a sequence addition of standard glimepiride solution (10^{-5}M) and the voltammogram was recorded for each addition (Fig. 7) under the previous optimum conditions (Table 3), the plot of peak current versus concentration (Fig. 8) gives a straight line with R^2= 0.997 and detection limit equal to 3.48×10^{-8}M.

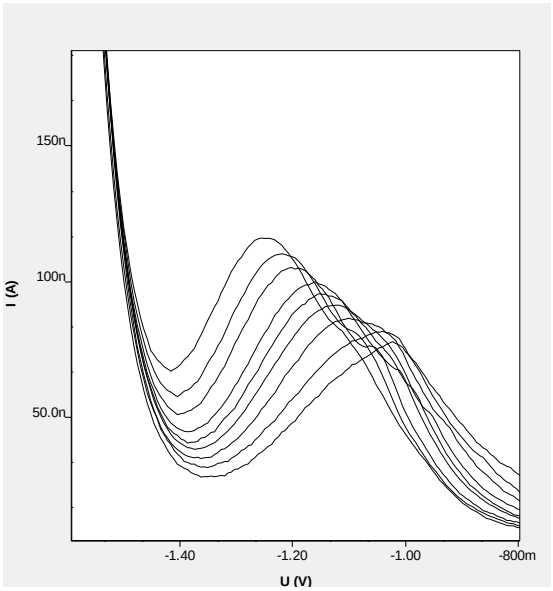

Fig. 7 Voltammograms of sequence addition of standard glimepiride solution (10^{-5}M) in phosphate buffer (pH=7)

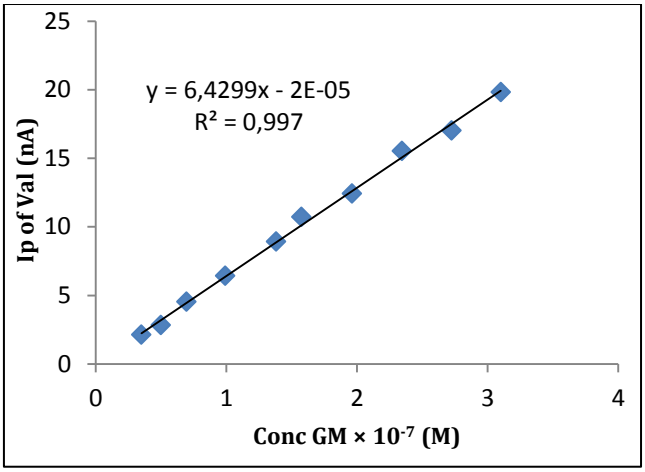

Fig. 8 The calibration curve of glimepiride using phosphate buffer (pH=7)

Interactions of valsartan with glimepiride

Square wave voltammograms of 1.4×10^{-5}M valsartan were recorded under the optimum conditions (Table 1) for a sequence additions of glimepiride solution at different temperatures using phosphate buffer pH=7 (human blood pH).

Stability of interaction

To study the stability of interaction peak a voltammogram of 1.9×10^{-4}M valsartan with 4.9×10^{-7}M glimepiride was recorded under the mentioned optimum conditions of valsartan (Table 1) in phosphate buffer pH=7 versus time, the results obtained are shown in table 5, it is clear that the interaction reduction peak current is stable within the time studied.

Table 5 Stability of interaction reduction peak current using phosphate buffer pH=7

Time (min)	Ip of Interaction (nA)
0	219
5	215
10	220
20	223
30	224
40	218
50	224

Binding constant

The decrease in peak current of valsartan with a sequence additions of glimepiride (Fig. 9) at all studied temperatures were noticed. The relations between reduction peak current and glimepiride concentrations added were linear at all studied temperatures with R^2 equal to 0.9943, 0.9964, 0.998, 0.9901, 0.991, 0.9903, 0.9412 and 0.9766 for 283^0, 289.5^0, 293^0, 298^0, 303^0, 308^0, 310^0 and 318^0K respectively. Thermodynamics parameters and binding constants were calculated (Table 6) according to equation (1) (Jalali and Dorraji, 2012) as shown in Figures 10-17.

$$ln\left(\frac{Ip}{\mathrm{Ip}^\circ - \mathrm{Ip}}\right) = ln\left(\frac{1}{[GM]}\right) - lnK \ldots . (1)$$

where K is the binding constant, Ip° and Ip are the reduction peak currents of the free valsartan and VAL-Glimepiride complex, respectively. The plot of ln(Ip/(Ip°-Ip)) versus ln(1/[GM]) is linear and the binding constant was obtained from its intercept.

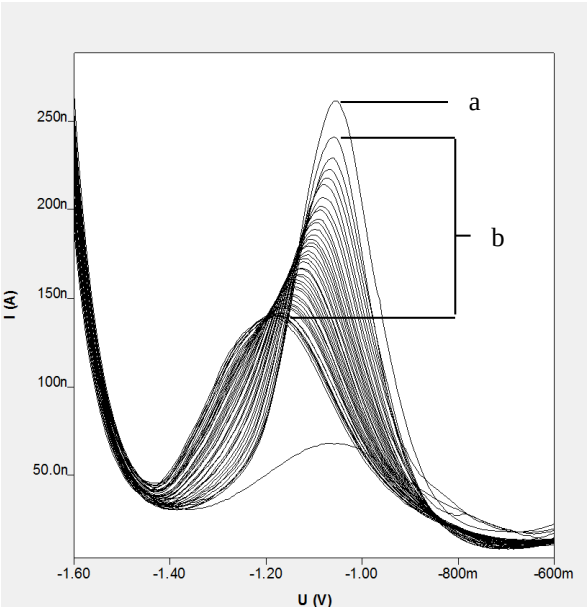

Fig. 9 The reduction peak of valsartan (a) with the sequence additions of glimepiride (b) at (293^{0}K)

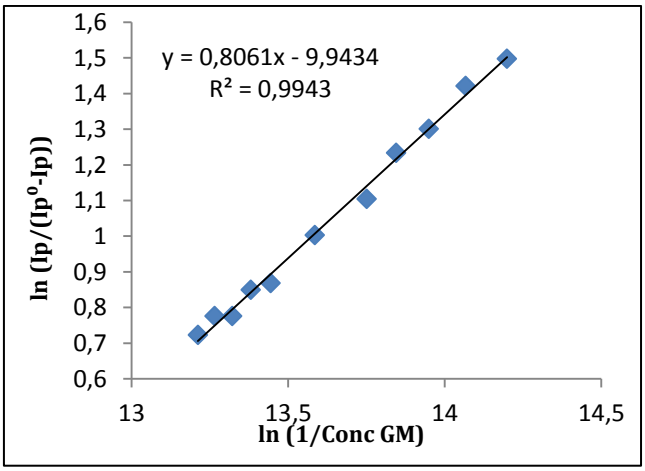

Fig. 10 ln (I p/(Ip^o –Ip)) vs ln (1/[Conc(M)]) at 283^{0}K

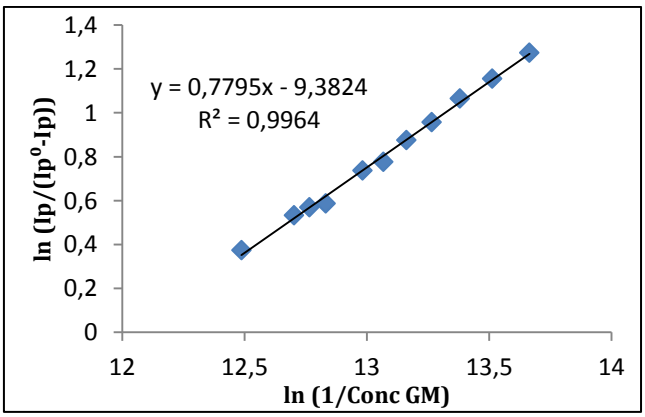

Fig. 11 ln (I p/(Ip^o –Ip)) vs ln (1/[Conc(M)]) at 289.5^{0}K

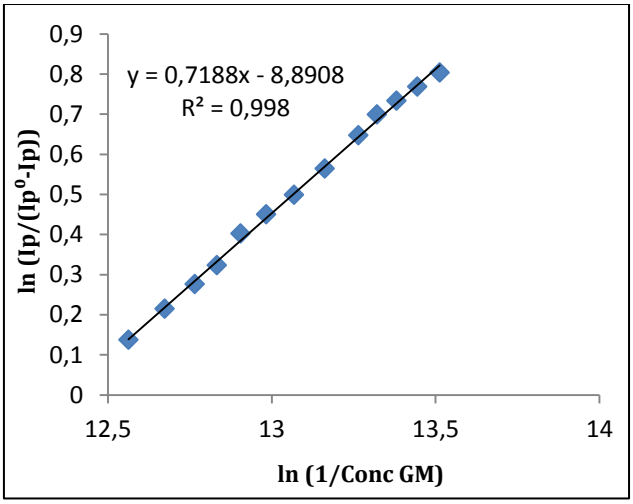

Fig. 12 ln (I p/(Ipº –Ip)) vs ln (1/[Conc(M)]) at 293^{0}K

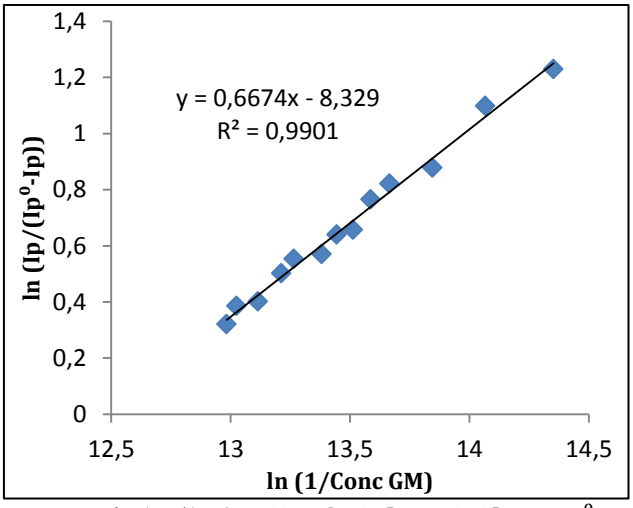

Fig. 13 ln (I p/(Ipº –Ip)) vs ln (1/[Conc(M)]) at 298^{0}K

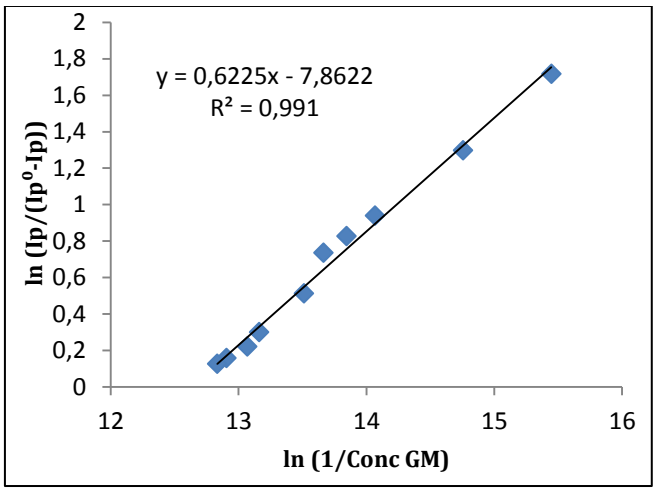

Fig. 14 ln (I p/(Ipº –Ip)) vs ln (1/[Conc(M)]) at 303^{0}K

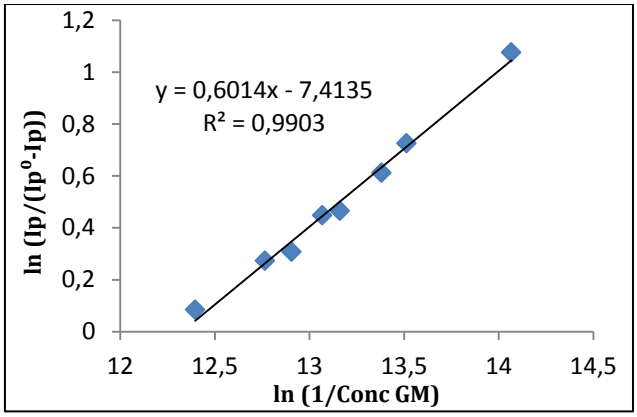

Fig. 15 ln (I p/(Ipº –Ip)) vs ln (1/[Conc(M)]) at 308^{0}K

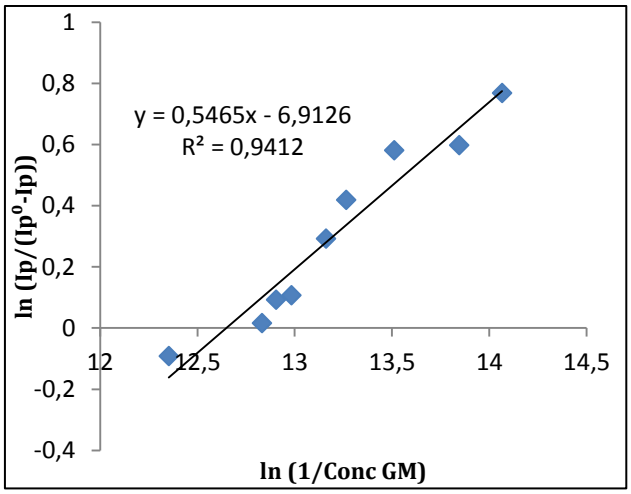

Fig. 16 ln (I p/(Ipº –Ip)) vs ln (1/[Conc(M)]) at 310^{0}K

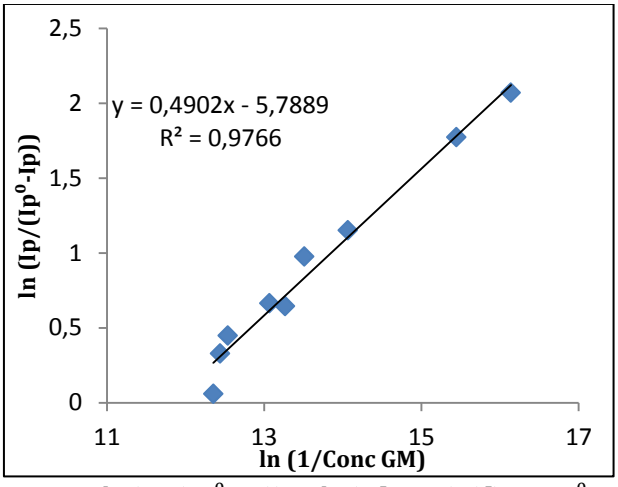

Fig. 17 ln (I p/(Ip^0 –Ip)) vs ln (1/[Conc(M)]) at 318^{0}K

Thermodynamics parameters

The plotting of ln K against 1/T using Van't Hoff equation (2), gives linear relationship (Fig. 18). The change enthalpy (ΔH) was obtained from the slope and other thermodynamics parameters (ΔG and ΔS) were calculated as follow:-

ln K = –ΔH/RT + ΔS/R …..(2)

Enthalpy (ΔH):-Based on the formula of Van't Hoff (3)

ΔH = - Slope × R …..(3) (R= 8.314 J. mole^{-1}. K^{-1})

The Free energy (ΔG) was calculated from the equation (4) of Van't Hoff described below:

$\Delta G = -R \times T \times \ln K$ …..(4)

Entropy ΔS was calculated from the intercept (5)

$\Delta S = \text{Intercept} \times R$ …..(5)

The plot of ln K versus 1/T gives straight line with R^2 equal to 0.9825 (Fig. 18).

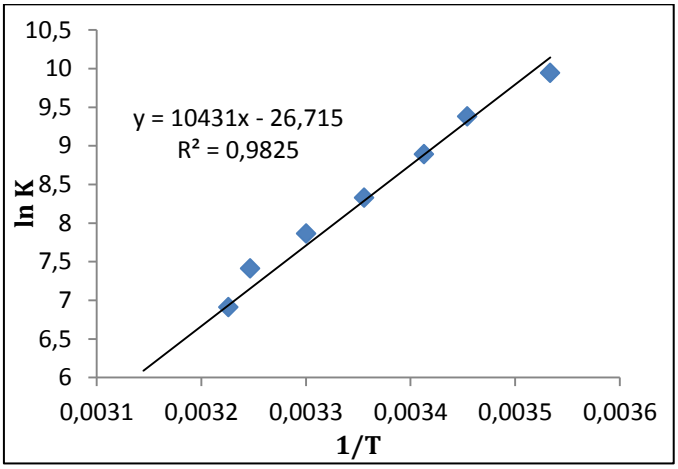

Fig. 18 Plot of ln K versus 1/T of interaction between valsartan and glimepiride

Table 6 Thermodynamics parameters and binding constants for valsartan and glimepiride interaction

Temp (K)	Binding constant (K_b) $\times 10^{-3}$ M^{-1}	ΔH ($KJ.mol^{-1}$)	ΔG ($KJ.mol^{-1}$)	ΔS ($J.mol^{-1}.K^{-1}$)
283	20.8	-86.7233	-23.3954	-222.1085
289.5	11.8		-22.5825	
293	7.26		-21.6580	
298	4.14		-20.6356	
303	2.59		-19.8059	
308	1.65		-18.9838	
310	1.00		-17.8161	
318	0.326		-15.3049	

The negative charge of ΔH indicates that the binding interaction is exothermic and binding constant decrease with increasing temperature, also ΔG become more positive with increasing temperature means the spontaneously of binding decreased, where as the negative value of ΔS indicate that the system became more ordered. The negative ΔH and ΔS values for the interaction of valsartan and glimepiride indicate that the binding is mainly enthalpy and entropy driven, and the interaction may involve hydrogen bonding and van der Waals forces played major role in the interaction (Ross and Subramanian, 1981).

Conclusion

Both valsartan and glimepiride gave a well-defined reduction peak at (-1.07)V, (-1.3)V respectivily on HMDE versus Ag/AgCl/sat.KCl in phosphate buffer solution using square wave voltammetry (SWV) technique. From studying the interaction of valsartan with glimepiride and calculate thermodynamics parameters, it was concluded that the interaction is exothermic and the system became more ordered due to the hydrogen bonding and van der Waals forces between the two drugs, and the interaction becomes non-spontinous with increasing temperature and the binding constant (K_b) decreases with increasing temperature too, this is consistent with the negative value of enthalpy.

Recommendations

Apply this study as standard method on pharmaceutical drugs and calculate the percentage of active substance in them.

Acknowledgements or Notes

Acknowledgements o my supervisor Asst. Prof. Dr. Amer Th. Al-Taee.

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