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Determination of Captopril Drug by Application of 1,10-Phenanthroline in the Spectrophotometric Technique

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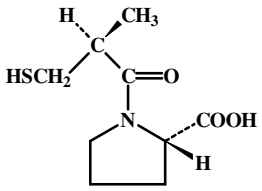
We carried out a new spectrophotometric method in order to determine captopril drug which is used as antihypertensive in tablet form. The method is based on the reduction of Fe^{3+} to Fe^{2+} by captopril, the resulting Fe^{2+} reacts with 1,10-phenanthroline to give a soluble orange-red complex in acidic medium. The maximal absorption is at the wavelength 510 nm. The linear relationship between the absorbance and the concentration of captopril was in the range of 1-35 mg/L with a correlation coefficient $R^2 = 0.999$. The detection limit is 1 mg/L, the molar absorption coefficient is 11865 L mol^{-1} cm^{-1}. This new method has offered a determination of captopril drug without any interference with excipients or hydrochlorothiazide either in raw material or in tablets indirectly with a high accuracy and an authenticity for the analytical results.

Key Words: Captopril, Hydrochlorothiazide 1,10-phenanthroline, Spectrophotometry.

INTRODUCTION

Captopril (**I**) is an antihypertensive drug, its scientific name is 1-(3-mercapto-2-D-methyl-1-oxoproppyl)-l-proline (S,S), (m.w. 217.29 g/mol).



I: Structure of captopril

Captopril dissolves well in distillated water, methanol, ethanol and other organic solvents. It is an angiotension-converting enzyme inhibitor which is extensively used for the treatment of hypertension, coronary heart disease and congestive heart failure[1] following myocardial infection and in diabetic nephropathy. About 60-75 % of a dose of captopril is absorbed from the gastro-intestinal tract and peak plasma concentration is achieved in *ca.* 1 h. About 30 % of the drug is bound to plasma protein[2].

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Captopril was determined either by direct or indirect methods, it was identified qualitatively and quantitatively by fluorimetry[3], chemiluminescence[4,5], HPLC[6-8], GC[9], GC-MS[10], spectrophotometry[11-14], flow injection analysis[15], kinetic spectrophotometry[16], FT-Raman spectroscopy[17], voltammetry[18], capillary electrophoresis[19-21], polarography[22], titrimetry[23] and polarimetry[24].

In this paper we presented a new spectrophotometric method in order to determine captopril using $FeCl_3$ as an oxidation agent, where Fe^{3+} will be reduced to Fe^{2+} by captopril, then the produced Fe^{2+} forms an orange-red complex with 1,10-phenanthroline, which is determined by spectrophotometric technique.

EXPERIMENTAL

UV-Visible spectrophotometer 503V Jasco (Japan), quartz cells 1 cm, analytical balance BP221S sartorious sensitivity 0.01, pH apparatus model 320 with Orion electrode, ultrasonic bath Powersonic 405 and pipettes product of HGB (Germany).

All reagents were high-pure, bi-distillated water, acetic acid, $FeCl_3$ and 1,10 phenanthroline produced by Merck company (Germany), captopril produced by chemical Oman company (Oman), hydrochlorothiazide product of Indenex company (India).

Indicator: 1,10-Phenanthroline is tricyclic aromatic component white crystalline, (m.p. 117 ºC, m.w. = 180 g/mol), slightly soluble in water, well soluble in some organic solvents as methanol, ethanol, acetone, benzene. It should be carefully used because it is toxic and carcinogenic. It is used as selective indicator for Fe^{2+} detection.

Drug products: we determined the quantity of captopril in some Syrian products, trade names: (Tensiopril (Rasha): captopril 25.5 mg/tablet, Capotal (Alpha) captopril 25.5 mg/tablet, Captomed (Medico): captopril 25.5 mg/tablet, Capoten (UniPharma): captopril 25.5 mg /tablet, Captophen (Ibn Hayan: captopril) 25.5 mg/tablet, Capo-Thiazide (Domina) captopril 25 mg and hydrochlorothiazide 12.5 mg/tablet and captopril 50 mg and hydrochlorothiazide 25 mg/tablet.

Reagents preparation

Captopril stock solution: The stock solution of captopril was prepared by dissolving 200 mg of captopril powder in clean and dried Becker, in 300 mL double distillated water and transformed to 1000 mL volumetric-flask and then adjusted to volume by double distillated water. We obtained a 200 mg/L of captopril stock solution.

Hydrochlorothiazide stock solution: The stock solution of hydrochlorothiazide was prepared by weighing 200 mg of hydrochlorothiazide powder in clean and dried Becker. It was dissolved in 40 mL of NaOH 0.1 M and 300 mL double distillated water and transformed to 1000 mL volumetric-flask, then adjusted to volume by double distillated water. We obtained a 200 mg/L of hydrochlorothiazide stock solution.

Indicator stock solution: We prepared the solution of 1,10-phenanthroline by weighing 39.64 mg of 1,10-phenanthroline. H_2O powder in clean and dried 100 mL

volumetric-flask, then adjusted to volume by double distillated water, it was put in ultrasonic bath for 1 h till completed dissolving. We obtained a 2×10^{-3} M of 1,10-phenanthroline stock solution.

Acetic acid stock solution: We prepared the stock solution of acetic acid by transforming 17.69 mL of acetic acid 96 % to 1000 mL volumetric-flask and then adjusted to volume by bi-distillated water. We obtained a 0.3 M acetic acid stock solution.

$FeCl_3$ stock solution: We prepared the solution of $FeCl_3$ by weighting 16.25 mg of $FeCl_3$ powder in clean and dried 100 mL volumetric-flask; it was dissolved in 5 mL of 0.3 M acetic acid stock solution and 30 mL bi-distillated water at first and then adjusted to volume by bi-distillated water. We obtained a 1×10^{-3} M $FeCl_3$ stock solution.

RESULTS AND DISCUSSION

At first step, Fe^{3+} was reduced by captopril to Fe^{2+} as it is shown in the following equation.

$$2C_9H_{14}NO_3S\text{-}H + 2Fe^{3+} \rightarrow C_9H_{14}NO_3S\text{-}SO_3NH_{14}C_9 + 2Fe^{2+} + 2H^+$$

At second step, Fe^{2+} was formed an orange-red complex by reacting between Fe^{2+} and 1,10-phenanthroline ($C_{12}H_8N_2$ = 180.2) (the indicator does not react with Fe^{3+}), as the suggested equation:

$$Fe^{2+} + 3C_{12}H_8N_2 \rightarrow [Fe(C_{12}H_8N_2)_3]^{2+}$$

Orange-red complex spectra: We traced the orange-red complex spectra at the wavelength range 415-600 nm, for the concentrations range between 1-30 mg/L of captopril against the blank solution prepared exactly by the same way but without captopril drug, using a quartz cell 1 cm. The spectra (Fig. 1) reveals a maximal absorption wavelength at 510 nm, with molar absorption coefficient 11865 L mol^{-1} cm^{-1}.

We studied all the parameters of the colored complex formation to obtain the optimal conditions as the following:

Effect of time: To study the time influence on the coloured complex formation, we transformed to 25 mL volume flask, 2 mL stock acetic acid 0.3 M, 5 mL double distilled water, 2.5 mL captopril solution 200 mg/L to obtain a final concentration of captopril 20 mg/L, 3 mL $FeCl_3$ of 1×10^{-3} M, 5 mL 1,10-phenanthroline of 2×10^{-3} M, respectively and completed to volume by double distilled water. The absorbance was measured at 510 nm in several times during 140 min against the blank prepared at same way without the drug. It is found that the completed coloured complex formation was after 25 min as shown in Fig. 2.

Effect of acetic acid volume: We studied the acetic acid 0.3 M volume influence on the coloured complex formation, we made a series of 25 mL volume flasks, contains each one between (0.5-5.0) mL of stock acetic acid 0.3 M, 5 mL double distilled, 2.5 mL captopril solution 200 mg/L, 3 mL $FeCl_3$ 1×10^{-3} M and 5 mL of

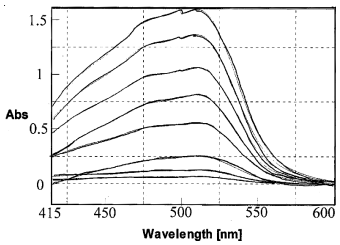

Fig. 1. Spectra of complex Fe^{2+}-1,10-phenanthroline concentrations in the range1-30 mg/L of captopril

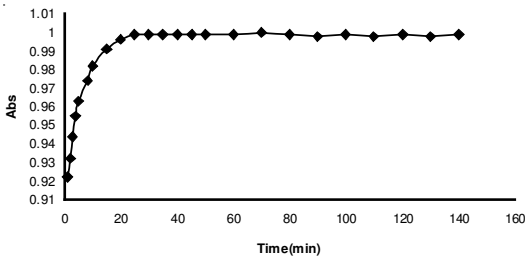

Fig. 2. Effect of the time on the coloured complex formation

1,10-phenanthroline 2×10^{-3} M, respectively, we completed to volume by double distilled water. We measured the absorbance at 510 nm for every added acetic acid volume, against (the blank prepared at same way without the drug). It is found that the completed colored complex formation took place after addition of 1.2 mL of acetic acid solution as it is shown in Fig. 3.

Effect of $FeCl_3$ solution volume: We studied the effect of 1×10^{-3} M $FeCl_3$ volume influence on formation of coloured complex, we transformed to 25 mL volume flask, 2 mL stock acetic acid 0.3 M, 5 mL double distilled water, 2.5 mL captopril solution 200 mg/L, variable volumes between (0.5-5.0) mL of 1×10^{-3} M $FeCl_3$ and 5 mL 1,10-phenanthroline of 2×10^{-3} M, respectively and completed to volume by bi-distillated water. The absorbance was measured at 510 nm in variable volumes against the blank prepared at same way without the drug, it is found that the completed coloured complex formation was after 2.5 mL $FeCl_3$ solution (Fig. 4).

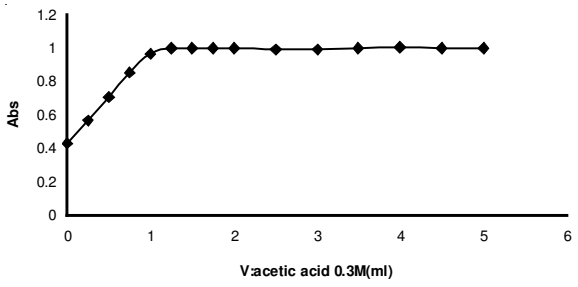

Fig. 3. Effect of 0.3 M acetic acid volume

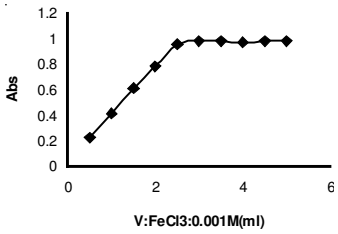

Fig. 4. Effect of $FeCl_3$ volume

Effect of 1,10-phenanthroline volume: The 1,10-phenanthroline volume influence on the colored complex formation was also studied. A series of 25 mL volume flasks, contains each one between (0.5-6.0) mL of 1,10-phenanthroline 2×10^{-3} M, 2 mL acetic acid 0.3 M, 5 mL double distilled, 2.5 mL captopril solution 200 mg/L and 3 mL $FeCl_3$ 1×10^{-3} M, respectively and completed the volume by double distilled water. The absorbance was measured at 510 nm for every added 1,10-phenanthroline volume, against the blank prepared at same way without the drug.

It is found that the completed colored complex formation was after 3.5 mL of 1,10-phenanthroline of 2×10^{-3} M (Fig. 5).

Linearity: We studied the linearity captopril concentration at the optimal conditions where we transform to 25 mL volume flask, 2 mL acetic acid, 5 mL double distilled water, in variable concentration range of captopril stock solution (200 mg/L) between 0.5-45.0 mg/L, 7 mL $FeCl_3$ of 1×10^{-3} M and 10 mL 1,10-phenanthroline 2×10^{-3} M and completed the volume by double distilled water. The absorbance was measured at 510 nm for each concentration against the blank prepared at same way without the drug, we found that linearity was good and obeyed Beer-Lambert Law in concentrations range (1-35) mg/L, correlation, coefficient $R^2 = 0.999$, m = 0.048 (Fig. 6).

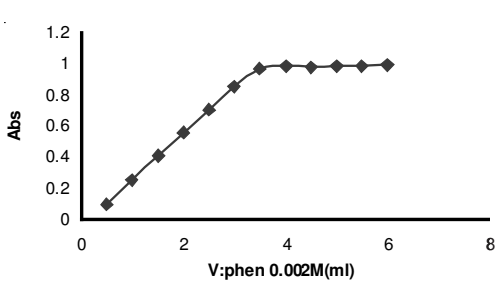

Fig. 5. Effect of 1,10-phenanthroline volume

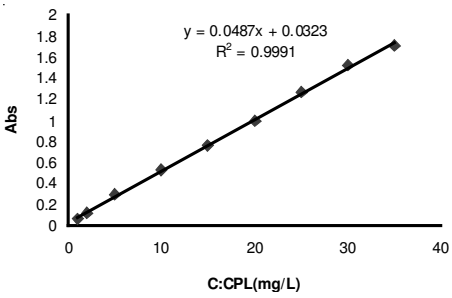

Fig. 6. Calibration curve for captopril concentrations range 1-35 mg/L

Furthermore, the hydrochlorothiazide spectrum in UV range 215-400 nm was studied in concentrations range between (1-50) mg/L, prepared from hydrochlorothiazide 200 mg/L stock solution, it is found that maximal absorbance peak appears at 274.5 nm as reveals in Fig. 7.

Fig. (8-a,b) represent the spectra of the captopril and hydrochlorothiazide which were dissolved each in 4 mL NaOH 0.1 M in 100 mL volumetric-flask, completed to volume with double distilled water, against the blank solution of 4 mL NaOH 0.1 M in 100 mL volumetric-flask, completed to volume with double distilled water to obtain 20 mg/L of each. It is noticed that a maximal absorbance peak at 274.5 nm for hydrochlorothiazide and not significant spectrum for captopril in UV field, which permits us to determine both of them at the same time at 274.5 nm for hydrochlorothiazide and at 510 nm as a captopril coloured complex.

Analysis application in commercial tablets: The proposed method has been applied for the analysis of captopril in their commercial tablets either alone or with hydrochlorothiazide. Ten tablets were grinded and determined the tablet average weight. A quantity of powder equal to 25 mg captopril is transferred to 100 mL volumetric-flask and completed to volume with bi-distillated water in the case of captopril alone, but in the case of combination of hydrochlorothiazide with captopril,

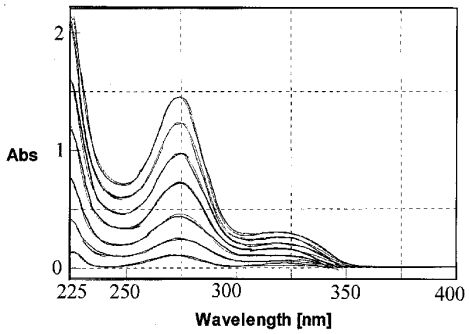

Fig. 7. Spectra of hydrochlorothiazide concentrations in the range 1-30 mg/L

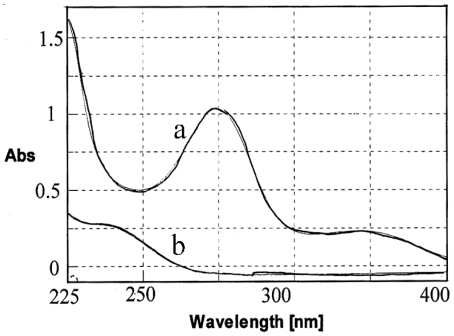

Fig. 8. Spectra of hydrochlorothiazide (a) and captopril (b) at concentration 20 mg/L for each

we added a quantity of powder equal to 12.5 mg hydrochlorothiazide and 25 mg captopril, then it is transformed a volume of 4 mL NaOH 0.1 M and completed to volume with double distilled water. The volumetric-flasks were put in ultrasonic bath for 0.5 h to have a complete captopril dissolving with concentration of 250 mg/L captopril and for the combination 250 mg/L captopril and 125 mg/L hydrochlorothiazide respectively. Centrifuge a sufficient quantity of precedent solution with speed = 3000 rpm for 10 min and take to 25 mL volumetric-flask 2 mL acetic acid 0.3 M, 5 mL double distilled water, 2 mL of supernatant captopril solution 250 mg/L (its final concentration in solution = 20 mg/L), 7 mL $FeCl_3$ 1×10^{-3} M and 10 mL 1,10-phenanthroline 2×10^{-3} M, respectively, we completed to volume by water. The absorbance of captopril samples was measured at 510 nm against the blank prepared at same way without the drug without any excipients interference and measured the absorbance of hydrochlorothiazide sample at 274.5 nm against the blank solution of 4 mL NaOH 0.1 M in 100 mL volumetric-flask, completed to volume with double distilled water. There were no interferences either with excipients neither with captopril. Table-1 presents the determination results of captopril and hydrochlorothiazide in some Syrian commercial products.

Conclusion

A new simple sensitive spectrophotometric method has been developed for captopril determination, by reducing Fe^{3+} to Fe^{2+} by captopril and the result Fe^{2+} reacts with 1,10-phenanthroline to give a soluble orange-red complex, where the UV spectrum of captopril does not have a significant feature. The proposed visible spectrophotometric method resolved this problem in addition to its rapidity, accuracy and precision as an indirect determination of captopril either for raw material or tablets without any interference with excipients with or without the presence of hydrochlorothiazide. We could also determine the hydrochlorothiazide with combination with captopril at UV field without any interference either with excipients neither with captopril.

TABLE-1
RESULTS OF DETERMINATION OF CAPTOPRIL AND HYDROCHLOROTHIAZIDE IN SOME SYRIAN DRUGS

Trade name	Company	CPL Dose (mg)	X_1	X_2	X_3	X_4	X_5	$\overline{X}$	Rec. (%)	RSD (%)
Tensiopril	Rasha	25.0	24.6	24.5	25.3	24.8	25.1	24.86	99.44	2.06
Tensiopril	Rasha	50.0	49.2	49.6	49.8	50.2	49.3	49.62	99.24	0.81
Capotal	Alpha	25.0	25.2	24.5	24.4	24.4	24.3	24.56	98.24	1.48
Capotal	Alpha	50.0	51.2	50.8	50.7	51.1	49.8	50.72	101.44	0.54
Captomed	Medico	25.0	25.5	25.3	24.6	25.0	24.8	25.04	100.16	1.45
Captomed	Medico	50.0	50.5	49.9	50.6	49.2	49.0	49.84	99.68	1.46
Capoten	U. Pharma	25.0	24.2	24.8	25.5	24.5	24.8	24.76	99.04	0.53
Capoten	U. Pharma	50.0	50.8	50.2	50.8	51.0	50.6	50.68	101.36	0.60
Captophen	Ibn Hayan	25.0	24.7	25.3	24.9	25.6	25.6	25.20	100.80	1.61
Captophen	Ibn Hayan	50.0	51.3	49.2	50.5	49.7	49.0	49.94	99.88	1.93
Capo-thiazide	Domina*	25.0	25.6	25.0	25.4	25.3	25.6	25.38	101.52	1.17
		12.5	12.2	12.3	12.7	12.4	12.2	12.36	98.88	1.68
Capo-thiazide	Domina*	50.0	49.8	49.2	50.5	49.0	49.3	49.56	99.12	1.22
		25.0	25.5	25.4	24.3	24.8	25.5	25.10	100.40	2.12

*: Hydrochlorothiazide, Captopril: CPL, Rec.: Recovery.

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