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Spectrophotometric Determination of Diltiazem Hydrochloride by Coloured Complex Formation

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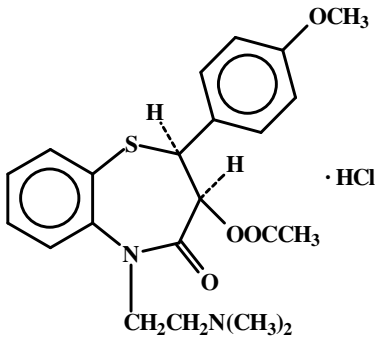
In present studies, a new spectrophotometric method is developed in order to determine diltiazem hydrochloride which is used as antihypertensive in tablet form. The method is based on the reaction between diltiazem hydrochloride and bromocresol purple to give a yellow complex in acidic medium. The yellow complex is extracted by chloroform. The maximal absorption is at wavelength 408 nm. The linear relationship between the absorbance and the concentration of diltiazem hydrochloride was in the range of (1-20) mg/L with a correlation coefficient R^2 = 0.999. The detection limit is 0.5 mg/L, the molar absorption coefficient was 37175 L mol^{-1} cm^{-1}. This new method has offered a determination of diltiazem hydrochloride without any interference with excipients either in raw material or in tablets with a high accuracy and an authenticity for the analytical results.

Key Words: Diltiazem hydrochloride, Bromocresol purple, Spectrophotometry.

INTRODUCTION

Diltiazem hydrochloride (**I**) is cardio-hypertension drug, its scientific name is 1,5-benzothiazepin-4(5*H*)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, mono-hydrochloride, (+)-*cis*. (mw = 450.98 g/mol).



I: Structure of diltiazem hydrochloride

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Diltiazem hydrochloride dissolves well in distillated water, chloroform and methanol, it is not soluble in benzene. It contains not less than 98.5 % and not more than 101.5 % in its bulk powder[1], it is used for treatment of angina, hypertension and supraventricular arrhythmias[2,3] diltiazem hydrochloride was identified by HPLC-UV[4-8], near infrared FT Raman spectroscopy[9], GC-MS[10], GC with electron capture detection[11], thin layer chromatography[12], reversed phase HPLC[13], spectrophotometry[14].

In this paper we presented a new spectrophotometric method in order to determine diltiazem hydrochloride using bromocresol purple as an indicator in acidic medium, where diltiazem hydrochloride reacts with bromocresol purple, then a yellow complex formed and extracted by chloroform, which is determined by spectrophotometric technique.

EXPERIMENTAL

UV-Visible spectrophotometer 503 V Jasco (Japan), quartz cells 1 cm, analytical balance BP221S Sartorious sensitivity 0.01, pH apparatus mode l320 with Orion electrode, ultrasonic bath Powersonic 405 and pipettes product of HGB (Germany).

All reagents were high-pure, double distilled water, acetic acid, boric acid, phosphoric acid, sodium hydroxide, chloroform produced by Merck company (Germany), diltiazem hydrochloride produced by Ready's (India), bromocresol purple produced by Merck company (Germany).

Indicator: Bromocresol purple is an anionic indicator component purple crystalline, (m.p. 242 ºC, m.w. 540.22 g/mol), slightly soluble in water, well soluble in some organic solvents as methanol, ethanol and well soluble in sodium hydroxide forming a violet sodumic salt, it is also used as pH indicator (its colour is yellow when pH is less than 5.2, purple for pH in the range 5.2-6.8, violet when pH is more than 6.8).

Drug products: We determined the quantity of diltiazem hydrochloride in some Syrian products, trade names: [diltiazem (Amrit): diltiazem hydrochloride 60 mg/tablet, Diltiazem Retard (Amrit): diltiazem hydrochloride 90, 120 and 180 mg/capsule, Dilzem (Asia): diltiazem hydrochloride 60 and 90 mg/coated tablet, Altiazem (Unipharma): diltiazem hydrochloride 60 mg/tablet, Altiazem Retard (Unipharma): diltiazem hydrochloride 180 mg/capsule, Diltiazor Retard (Ibn Zahr): diltiazem hydrochloride 90 mg/capsule, Teldia (Bahry): diltiazem hydrochloride 60 mg/tablet Teldia Retard (Bahry): diltiazem hydrochloride 120 and 180 mg/capsule, Zilden (Pharmacir): diltiazem hydrochloride 60 mg/tablet, Adizem (Barakat): diltiazem hydrochloride 60 mg/tablet, Adizem Retard (Barakat): diltiazem hydrochloride 90 and 120 mg/capsule].

Diltiazem hydrochloride stock solution: The stock solution of diltiazem hydrochloride was prepared by dissolving 100 mg of diltiazem hydrochloride powder in clean and dried beaker, in 300 mL double distilled water and transformed to 1000 mL volumetric-flask and then adjusted to volume by double distilled water. We obtained a 100 mg/L of diltiazem hydrochloride stock solution.

Indicator stock solution: The solution of bromocresol purple was prepared by dissolving 54 mg of bromocresol purple powder in clean and dried beaker, in 2 mL NaOH 0.1 M and 20 mL double distilled water for 1 h and transformed to 100 mL volumetric-flask and then adjusted to volume by double distilled water. A stock solution of 1×10^{-3} M of sodium salt of bromocresol purple was obtained.

Britton-Robinson buffer solution: The Britton-Robinson buffer solution (universal buffer) was prepared by transforming 129 mL of each acetic acid 0.04 M, boric acid 0.04 M, phosphoric acid 0.04 M and 45.2 mL NaOH 0.2 M to 500 mL volumetric flask and then adjusted to volume by double distilled water. We obtained a 500 mL of Britton-Robinson buffer solution pH 2.

RESULTS AND DISCUSSION

At first step, diltiazem hydrochloride reacted with bromocresol purple to give a yellow complex in acidic medium. At second step the yellow complex was extracted by chloroform.

Yellow complex spectra: We obtained the yellow complex spectra at the wavelength range 350-500 nm after extraction by chloroform, for the concentrations range between 2-40 mg/L of diltiazem hydrochloride against the blank solution prepared exactly by the same way but without diltiazem hydrochloride drug, using a quartz cell 1 cm. The spectra (Fig. 1) reveals a maximal absorption wavelength at 408 nm, with molar absorption coefficient 37175 L mol^{-1} cm^{-1}.

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

Effect of buffer volume: To study the buffer volume influence on the coloured complex formation, we made a series of 50 mL separation funnels, contains each one between (0.1-5.0) mL of buffer, 2 mL diltiazem hydrochloride solution 100 mg/L and 3 mL bromocresol purple sodium salt 1×10^{-3} M, respectively, we completed to 15 mL by double distilled water (then the final concentration of diltiazem hydrochloride in solution is 13.33 mg/L or 20 mg/L in extracted chloroform). We extracted by chloroform for 3 times and transformed the organic phase to 10 mL volumetric flask and then adjusted to volume by chloroform for each solution. The absorbance at 408 nm was measured for every added buffer volume, against (the blank prepared at same way without the drug). It is found that the optimum buffer volume was in the range of (0.5-2.0) mL (Fig. 2).

Effect of indicator volume: To study the bromocresol purple volume influence on the coloured complex formation, in a series of 50 mL separation funnels, containing each one 1 mL of buffer, 2 mL diltiazem hydrochloride solution 100 mg/L and between (0.1-4.0) mL bromocresol purple sodium salt 1×10^{-3} M, respectively. We completed to 15 mL by double distilled water. The extraction was performed by chloroform for 3 times and transformed the organic phase to 10 mL volumetric flask and then adjusted to volume by chloroform for each solution. The absorbance at 408 nm for every added bromocresol purple sodium salt volume, against (the

blank prepared at same way without the drug). It is found that the completed coloured complex formation was obtained after 2.5 mL bromocresol purple sodium salt solution (Fig. 3).

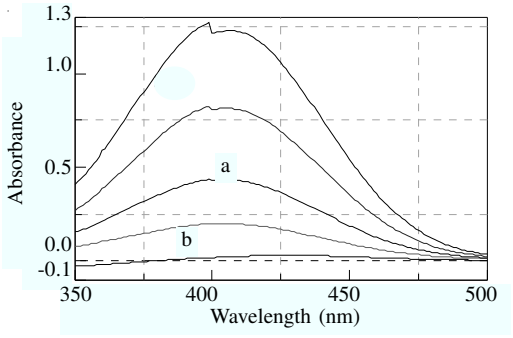

Fig. 1. (a) Spectra of diltiazem hydrochloride-bromocresol purple complex for concentrations range (2-15) mg/L of diltiazem hydrochloride (b) Blank

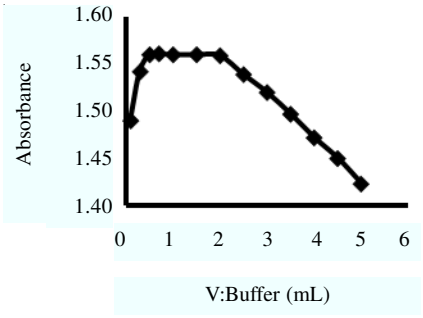

Fig. 2. Effect of buffer volume on diltiazem hydrochloride-bromocresol purple complex formation

Mole-ratio method: To study the reaction ratios between diltiazem hydrochloride and bromocresol purple, a series of 50 mL separation funnels was maintained containing each one 1 mL of buffer, 1 mL diltiazem hydrochloride solution 2×10^{-4} M equivalent to concentration of 2×10^{-7} M and between (0.1-3.0) mL bromocresol purple sodium salt 2×10^{-4} M, respectively, we completed to 15 mL by double distilled water. We extracted by chloroform for 3 times and transformed the organic phase to 10 mL volumetric flask and then adjusted to volume by chloroform for each solution. We measured the absorbance at 408 nm for every added bromocresol purple sodium salt volume, against (the blank prepared at same way without the drug). It is found that reaction ratio (diltiazem hydrochloride:bromocresol purple) was (1:1) (Fig. 4).

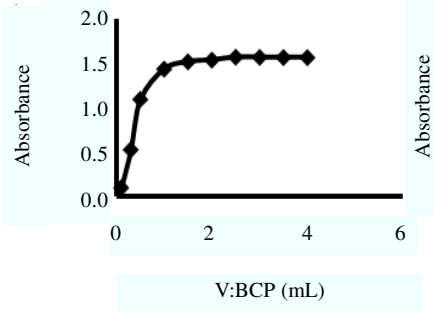

Fig. 3. Effect of bromocresol purple volume

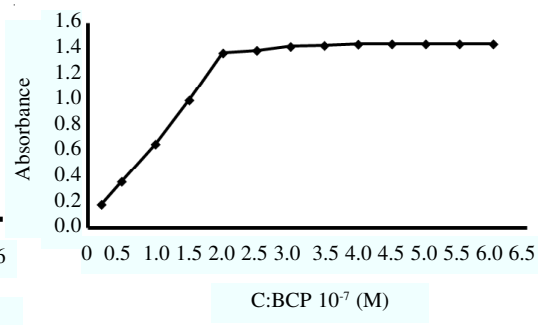

Fig. 4. Mole-ratio of diltiazem hydrochloride-bromocresol purple complex

Method of continuous ratios: To study the reaction ratios by continuous variation between diltiazem hydrochloride and bromocresol purple, we made a series of 50 mL separation funnels, contains each one 1 mL of buffer, X mL diltiazem hydrochloride solution 2×10^{-4} M and Y mL bromocresol purple sodium salt 2×10^{-4} M (always X + Y = constant), respectively, we completed to 15 mL by double distilled water. We extracted by chloroform for 3 times and transformed the organic phase to 10 mL volumetric flask and then adjusted to volume by chloroform for each solution. The absorbance at 408 nm was measured for every added diltiazem hydrochloride and bromocresol purple sodium salt volume, against (the blank prepared at same way without the drug). It is found that reaction ratio (diltiazem hydrochloride:bromocresol purple) was (1:1) (Fig. 5).

Linearity: We studied the linearity diltiazem hydrochloride concentration at the optimal conditions where a series of 50 mL separation funnels was performed containing each one 1 mL of buffer, in variable concentration of diltiazem hydrochloride stock solution (100 mg/L) between (0.2-30.0) mg/L, 4 mL bromocresol purple sodium salt 1×10^{-3} M, respectively, we completed to 15 mL by double distilled water. We extracted by chloroform for 3 times and transformed the organic phase to 10 mL volumetric flask, then adjusted to volume by chloroform for each solution. The absorbance was measured at 408 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 (1-20) mg/L, correlation coefficient $R^2 = 0.999$, m = 0.076 as it is shown in Fig. 6.

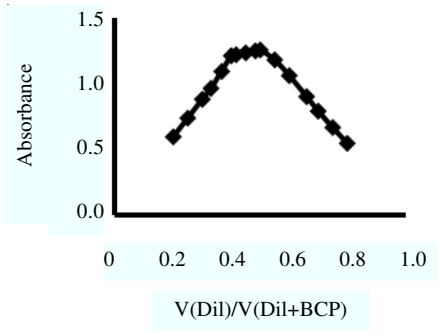

Fig. 5. Reactions ratio by continuous variation method

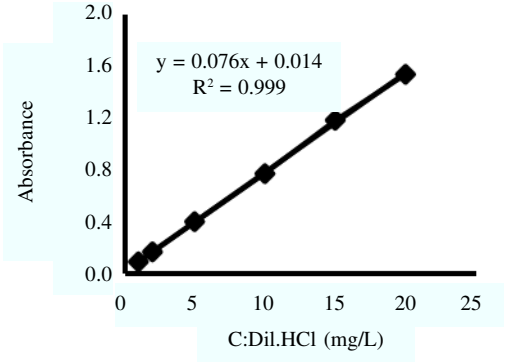

Fig. 6. Calibration curve for diltiazem hydrochloride concentrations range (1-20) mg/L

Analysis application in commercial tablets: The proposed method has been applied for the analysis of diltiazem hydrochloride in their commercial tablets. Ten tablets were grinded and determined the tablet average weight. A quantity of powder equal 25 mg diltiazem hydrochloride to 250 mL volumetric-flask and completed to volume with double distilled water. Centrifuge a sufficient quantity of precedent solution with speed 3000 rpm for 10 min and take to 50 mL separation funnel 1 mL

of buffer, 1.5 mL of supernatant diltiazem hydrochloride solution (its final concentration in solution 10 mg/L) and 3 mL bromocresol purple sodium salt 1×10^{-3} M, respectively, we completed to 15 mL by double distilled water. We extracted by chloroform for 3 times and transformed the organic phase to 10 mL volumetric flask and then adjusted to volume by chloroform for each solution. The absorbance of diltiazem hydrochloride samples was measured at 408 nm for every added diltiazem hydrochloride volume, against (the blank prepared at same way without the drug). There were no interferences with excipients except altiazem retard (Uni-pharma company). Table-1 presents the determination results of diltiazem hydrochloride in some Syrian commercial products.

TABLE-1
RESULTS OF DETERMINATION OF DILTIAZEM HYDROCHLORIDE IN SOME SYRIAN DRUGS

Trade name	Company	DIL dose (mg)	X_1	X_2	X_3	X_4	X_5	$\overline{X}$	Rec. (%)	RSD (%)
Altiazem	Uni pharma	60	59.6	61.9	62.0	61.7	60.8	61.2	102.0	1.8
Diltiazem	Amrit	60	61.9	60.9	59.4	61.8	60.3	60.9	101.4	1.5
Diltiazem retard	Amrit	90	91.3	91.8	88.7	91.0	91.5	90.9	100.1	1.3
Diltiazem retard	Amrit	120	124.3	122.9	121.7	123.0	122.8	122.9	102.4	0.7
Diltiazem retard	Amrit	180	181.3	179.0	181.4	184.2	181.7	181.5	100.8	1.0
Diltiazor retard	IbnZahr	90	90.0	90.8	91.6	88.3	91.5	90.4	100.5	1.5
Zilden	Pharmcir	60	60.7	61.5	58.5	58.8	59.9	59.9	99.8	2.6
Dilzem	Asia	60	59.5	58.8	60.5	618	61.4	60.4	100.7	2.2
Dilzem	Asia	90	87.5	89.0	88.8	90.0	87.9	88.6	98.4	1.1
Teldia	Bahry	60	59.9	58.6	61.5	60.0	58.8	59.8	99.6	1.9
Teldia retard	Bahry	120	117.7	119.1	118.5	119.8	121.0	119.2	99.3	1.0
Teldia retard	Bahry	180	177.0	178.2	182.6	176.9	178.6	178.7	99.2	1.3
Adizem	Barakat	60	60.4	61.0	58.9	60.7	58.7	59.9	99.9	1.8
Adizem retar	Barakat	90	89.3	89.9	91.6	92.0	92.2	91.1	101.1	1.4
Adizem retard	Barakat	120	124.4	121.3	122.6	123.4	119.6	122.2	101.9	1.5

DIL: Diltiazem hydrochloride, Rec: recovery.

Conclusion

A new simple spectrophotometric method has been developed for diltiazem hydrochloride determination, by reacting with bromocresol purple to give a yellow complex in acidic medium and extract this yellow complex by chloroform. The proposed visible spectrophotometric method offered a high sensitivity in addition to its rapidity, accuracy and precision as an indirect determination of diltiazem hydrochloride either for raw material or tablets without any interference with excipients.

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