SELECTIVE SPECTROPHOTOMETRIC DETERMINATION OF FENOTEROL BY THREE DIFFERENT METHODS.

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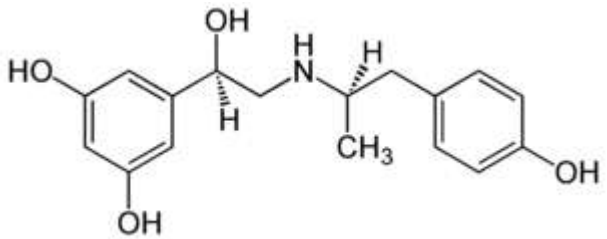
ABSTRACT:

Three simple and selective spectrophotometric methods were developed for the quantitative determination of Fenoterol in pure forms as well as in its pharmaceutical formulation. **Method [A]** Involves the coupling of the drug as phenolic compound with the diazonium salts of four amines, namely, Benzocaine (BZC), sulphadiazine (SDZ), sulphacetamide (SCM) and sulphanilic acid (SPA) forming red azodyes absorbed at 526, 514, 512 and 513 nm, respectively. Beer's law was obeyed in the concentration ranges of 10-70, 6-42, 4-28 and 3.5-24.5 μg ml^{-1} for the four reagents, respectively. **Method [B]** is based on reaction of Fenoterol with cobalt thiocyanate, where by a sparingly soluble blue ion-pair complex is formed. This complex is extracted by toluene and spectrophotometrically measured at 619 nm. Good linearity was obtained in the range of 10-70 μg ml^{-1}. **Method [C]** is based on the reduction of iron (III) by Fenoterol in acid medium and subsequent interaction of iron (II) with ferricyanide to form Prussian blue. The product exhibits absorption maximum at 730 nm. Beer's law was obeyed in the concentration range of 1.5–10.5 μg ml^{-1}. The reaction conditions for described methods were studied and optimized. The proposed methods were applied to the determination of Fenoterol in pharmaceutical formulation and the results demonstrate that the methods are equally accurate and precise as the reported methods found from the t and F values. The reliability of the methods was established by recovery studies using standard addition technique.

INTRODUCTION

Fenoterol (Fig. 1) is a direct acting sympathomimetic agent with predominantly beta-adrenergic activity and a selective action on β_2 receptors. It is used as bronchodilator, with its bronchodilating action being relatively more prominent than its effect on the heart. It is used in the treatment of bronchial asthma, prevention of exercise-induced bronchspasm and in the management of premature labour (**Kathleen, 1999)** .



1-(3, 5-dihydroxyphenyl)-2-(4-hydroxy-methylphenethylamino) ethanol hydrobromide

Fig.1

Different methods have been reported for the determination of Fenoterol such as spectrophotometric (**El-Shabrawy *et al.*, 2003; Negussie *et al.*, 2004; Zamuner *et al.*, 2008)**, spectrofluorimetric (**Manal, 2007; El-Tarras *et al.*, 2005)**, HPLC (**Danuta *et al.*, 2008; Ingolfe *et al.*, 2002)**, LC-MS (**Hee Seung, *et al.*, 2008)**, Capillary zone electrophoresis **(Somsak and Proespichaya, 2008)**, and electrochemical methods (**Belal *et al.*, 2000)**. The aim of the present study is to develop new, simple, and accurate quantitative methods for determination of fenoterol in both pure and pharmaceutical forms.

EXPERIMENTAL

1. Pure sample

Fenoterol hydrobromide (99.67%); was kindly supplied by Chemical Industries Development Company, (CID), Giza, Egypt.

2. Market sample

Berotec® Tablets: Product of Chemical Industries Development Company (CID) Cairo, Egypt. Batch No. (503104), labeled to contain 0.5 mg Fenoterol hydrobromide per tablet and purchased from local pharmacies.

3. Chemicals and Reagents:

All reagents used were of analytical grade, solvents were of spectroscopic grade and water was freshly double-distilled.

- Sodium hydroxide, hydrochloric acid, ethanol, cobalt chloride, ammonium thiocyanate, toluene, chloroform, methylene chloride, benzene, ferric chloride, potassium ferricyanide and methanol (El-Nasr Company , Egypt) (ADWIC).
- Sodium nitrite (Winlab-UK) 1% aqueous solution.
- Sodium hydroxide 0.2 N and 1N aqueous solution.
- Benzocain 0.1% in ethanol (Sigma, U.S.A).
- Hydrochloric acid 0.1N aqueous solution.
- Sulphadiazine 0.1% in ethanolic 0.1N HCl (Sigma, U.S.A)
- Sulphacetamide 0.1% in ethanol (Sigma, U.S.A)
- Sulphuric acid 1 M and 10 M aqueous solution (Merck-Germany).
- Sulphanilic acid 1% aqueous solution, (ADWIC, Egypt)
- Cobalt thiocyanate (prepared by mixing 56.25 gm NH_4SCN with 13.80 gm $CoCl_2$ in H_2O to give 100 ml of the solution **(Nerin et al., 1985).**
- Ferric chloride 0.2% and potassium ferricyanide 0.2% aqueous solutions.

4. Apparatus:

Shimadzu, UV-Vis 1650 PC spectrophotometer, equipped with 10 mm matched quartz cells.

5. Standard solutions:

For method **A** and **C**, stock solutions of Fenoterol (1 mg ml^{-1}) were prepared by dissolving 100 mg powder of Fenoterol in 100 ml water. For method B the stock solutions of Fenoterol (1 mg ml^{-1}) were prepared by dissolving 100 mg powder in 100 ml methanol. Solutions with different concentrations were prepared from the stock solution by suitable dilutions.

6. Procedure:

6.1. Method A (Diazo-coupling technique):

6.1.1. Construction of calibration graphs:

In a series of 10 ml volumetric flasks a volume of 0.5 ml of amine compounds 0.1% BZC, 0.1% SDZ, 0.1% SCM and 1% SPA was mixed with 0.5 ml of 0.1 N hydrochloric acid and 1 ml of $NaNO_2$ solution (1%) and the mixture was left to stand for 10 min. different aliquots of the standard solution of Fenoterol equivalent to (100-700 µg), (60-420 µg), (40-280 µg) and (35-245 µg) were added to the diazo-reagent formed by BZC, SDZ, SCM and SPA respectively. The calibration curve representing the relationship between the absorbance and the corresponding concentrations were constructed and the corresponding regression equations were computed.

Then 0.5 ml of 0.2 N sodium hydroxide was added dropwise to each flask and the volume was adjusted to the mark with ethanol, the absorbance of the red coloured formed was measured at 526, 514, 512 and 513 nm for BZC, SDZ, SCM and SPA acid respectively.

N.B.: In case of sulphadiazine, hydrochloric acid was omitted where the amine dissolved in ethanolic 0.1 N HCl and in case of sulphanilic acid hydrochloric acid was not necessary as the amine is acidic in nature.

6.1.2. Determination of the stoichiometry of the reaction by Molar ratio method (Rose, 1964)

In a series of 25 ml volumetric flasks, different volumes (1-10 ml) of BZC solution (4.12×10^{-5} M), SDZ solution (2.47×10^{-5}M), SCM solution (1.64×10^{-5} M) and SPA solution (1.44×10^{-5} M) were mixed with 1 ml of 0.1 N hydrochloric acid (in case of BZC and SCM) and 2 ml of sodium $NaNO_2$ solution (1%) the mixture were left to stand for 10 minutes, 1 ml of Fenoterol solution (4.12×10^{-5} M), (2.47×10^{-5}M), (1.64×10^{-5} M) and (1.44×10^{-5} M), respectively were added to each flask followed by 1 ml of 0.2 N sodium hydroxide, again stay for 5 minute, complete the volume to the mark with water and measure the absorbencies at their corresponding λ_{max}.

6.2. Method B: (Ion-pair technique)

6.2.1. Construction of calibration graphs

Aliquots of standard solution equivalent to (100-700 µg) were transferred quantitatively to 50 ml separating funnels followed by 4 ml of cobalt thiocyanate reagent. The solutions were mixed and the formed blue coloured complexes were extracted with 10 ml of toluene. The organic extract was collected in 10 ml volumetric flask and completed to volume with toluene. Absorbencies were measured at 619 nm. The calibration curve representing the relationship between the absorbance and the corresponding concentrations were constructed and the corresponding regression equations were computed.

6.2.2. Determination of the stoichiometry of the reaction by Molar ratio method (Rose, 1964):

In a series of 50 ml separating funnels, deferent volumes (0.5-5 ml) of cobalt thiocyanate reagent (1.64×10^{-5} M) were added to 1 ml Fenoterol (1.64×10^{-5} M). The solutions were mixed and the formed blue coloured complexes were extracted with 10 ml of toluene. The organic extract was collected in 10 ml volumetric flask and completed to volume with toluene and the absorbances were measured at 619 nm. The calibration curve representing the relationship between the absorbance and the corresponding concentrations were constructed and the corresponding regression equations were computed.

6.3. Method C: (Prussian blue technique):

Construction of calibration graphs:

Into a series of 10 ml volumetric flasks different aliquots (15-105) µg ml^{-1} of Fenoterol were transferred and the total volume of each flask was adjusted to 3 ml by adding water. Then 2 ml each of $FeCl_3$ (0.2%) and ferricyanide (0.2%) were added to each flask, mixed well and let to stand for 10 min. finally, 1 ml of 10 M H_2SO_4 was added to each flask and diluted to mark with water and mixed well. The absorbance of the resulting blue colored solutions were measured at 730 nm against a reagent blank prepared similarly. The calibration curve representing the relationship between the absorbance and the corresponding concentrations were constructed and the corresponding regression equations were computed.

7. Analysis of tablets:

The contents of 10 tablets of Fenoterol were weighed and powdered. A quantity of the powder equivalent to 100 mg was transferred into 100 ml volumetric flask and shaked with 20 ml water for about 10 min. the volumes were adjusted with water and filtered in methods **A** and **C**, while in method **B** shaked with 20 ml methanol for about 10 min, and the volume was completed to 100 ml by methanol and filtered. Analysed aliquots of the clear filtrate, labeled to contain (1 mg ml^{-1}), suitably diluted and subjected to procedures **A, B,** and **C**.

RESULTS AND DISCUSSION

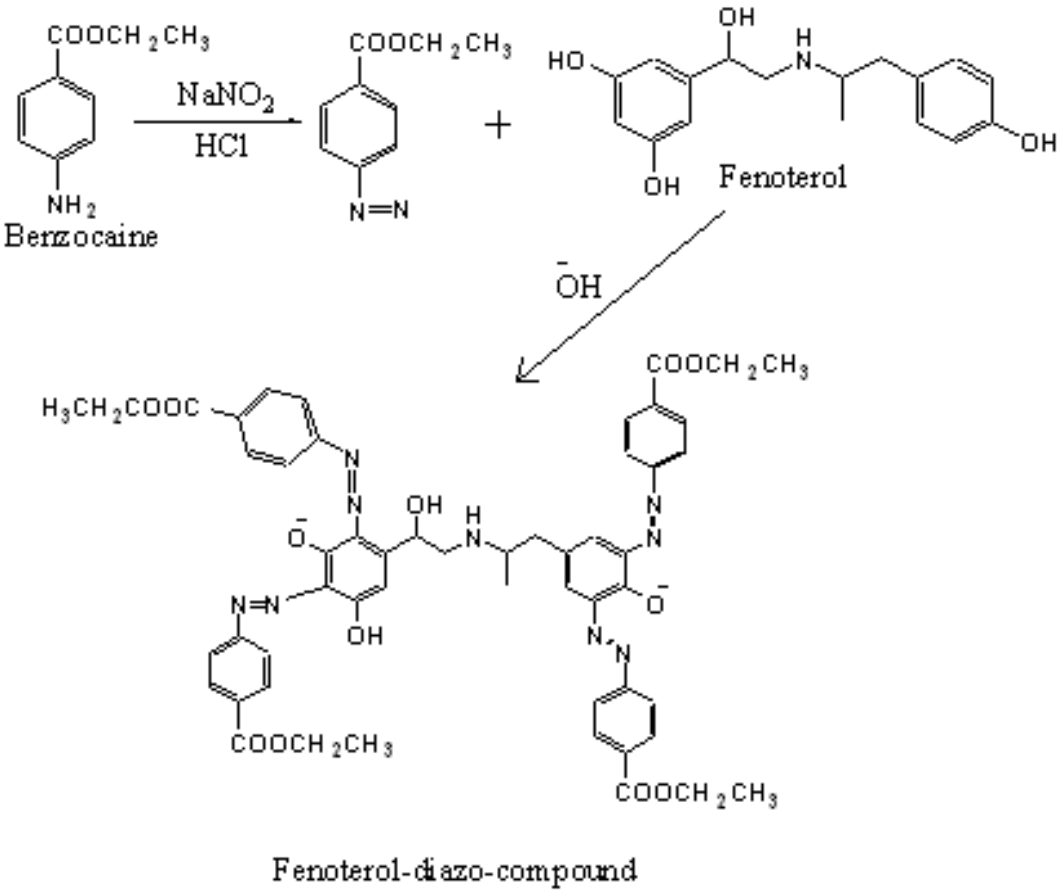
Method A (Diazo-coupling technique):

The utility of diazotized different amines BZC, SDZ, SCM and SPA as chromogenic reagents for the determination of the phenolic drug was investigated in the present study. The stability of the complex formed maintained by the use of 0.5 ml of (0.1%) BZC, (0.1%) SDZ, (0.1%) SCM and (1%) SPA, as shown in (figure 6), 0.5 ml hydrochloric acid (0.1N) in case of BZC and SCM, as shown in (figure 7), 0.5 ml $NaNO_2$ (1%) solution, as shown in (figure 8), making the medium alkaline with 0.5 ml NaOH (0.2N) solution, as shown in (figure 9). The reaction mixtures were allowed to stand 5 min. before adjusting volumes with ethanol and measuring the absorbencies at their λ_{max} which were 526, 514, 512 and 513 nm for BZC, SDZ, SCM and SPA, respectively as shown in (Figures 2,3,4,5). The colour intensities were found to be stable for more than one hour, under the optimum experimental conditions. The calibration graphs were constructed for the determination of Fenoterol by the proposed technique where Beer's law was obeyed in the ranges of (10-70), (6-42), (4-28) and (3.5-24.5) µgml^{-1} for (BZC), (SDZ) (SCM) and (SPA), respectively. The stoichimetric ratio determined by molar ratio indicated that the ratio of the drug to reagent is 1:4 as shown in (figure 10), the proposed mechanism for the diazo-coupling reaction with BZC is shown in (scheme 1). The regression equations, LOD, LOQ and response factor in addition to A (1%, 1cm.) were illustrated in table (1).

Table (1): Selected spectral data for the determination of Fenoterol by the proposed procedures:

Method	***A***				***B***	***C***
	BZC	SDZ	SCM	SPA		
λ_{max} nm	526	514	512	513	619	730
Linearity range (μgml^{-1})	10-70	6-42	4-28	3.5-24.5	10-70	1.5-10.5
LOD (μgml^{-1})	0.188	0.2303	0.0586	0.0313	0.117	0.0102
LOQ (μgml^{-1})	0.627	0.7678	0.1955	0.1044	0.392	0.0343
Response factor ± SD	0.0145 ±0.0002	0.0225 ±0.0003	0.03546 ±0.0004	0.0393 ±0.0003	0.0126 ±0.0002	0.0907 ±0.001
A (1%, 1 cm)	145.04	223.78	351.5	392.23	126.37	908.33
Regression Parameters						
- ***Slope***	0.01398	0.02161	0.0343	0.0380	0.0125	0.0903
- Intersept	0.01325	0.01154	0.0111	0.0105	0.0036	0.0022
- Correlation Coeff(r^2)	0.9997	0.9996	0.9996	0.9996	0.9997	0.9996

Reaction mechanism was suggested to be as follow:



Fenoterol-diazo-compound

Scheme 1: The suggested reaction pathway of Fenoterol with diazotized BZC

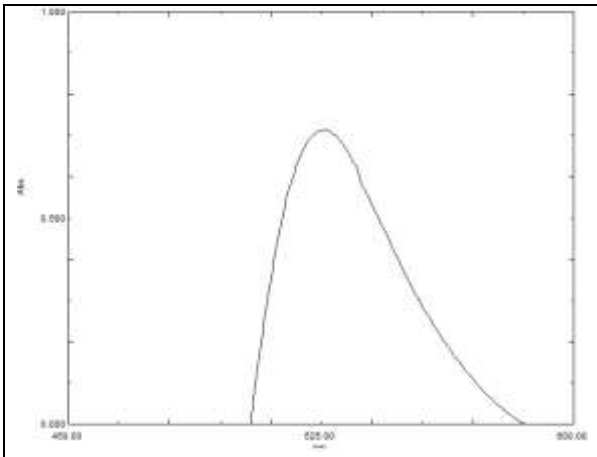


Figure (2): Absorption spectrum of Fenoterol (50 μgml^{-1}) with Diazotized Benzocain

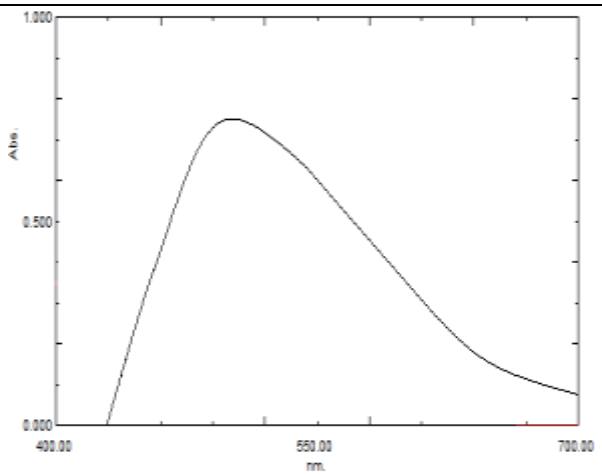


Figure (3): Absorption spectrum of Fenoterol (30 μgml^{-1}) with Diazotized Sulphadiazine

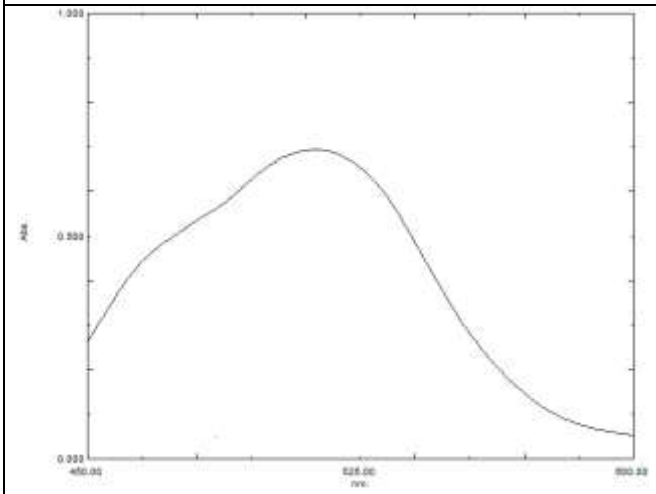


Figure (4): Absorption spectrum of Fenoterol (20 μgml^{-1}) with Diazotized Sulphacetamide

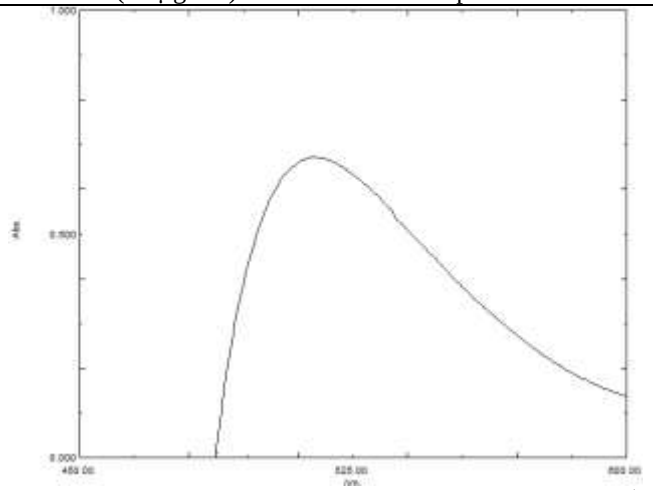


Figure (5): Absorption spectrum of Fenoterol (17.5 μgml^{-1}) with Diazotized Sulphanilic acid

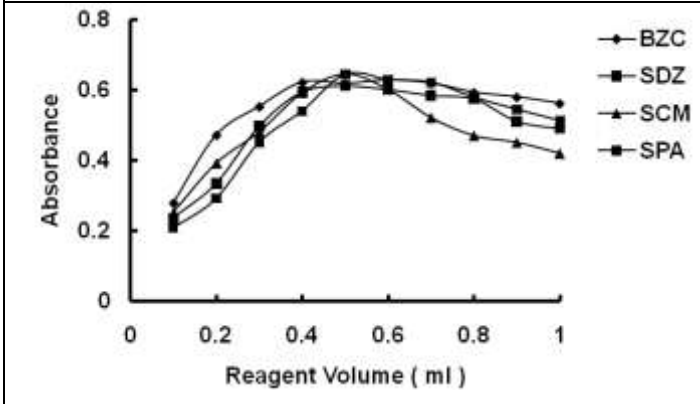


Figure (6) : Effect of volume of amine on absorbance of the formed reaction product with Fenoterol

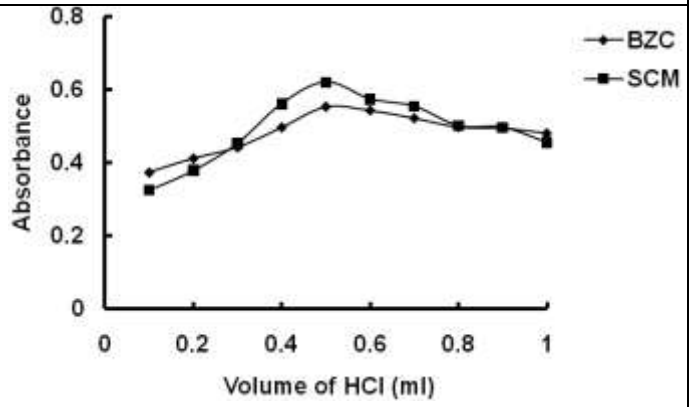


Figure (7): Effect of volume of acid on absorbance of formed reaction product with Fenoterol

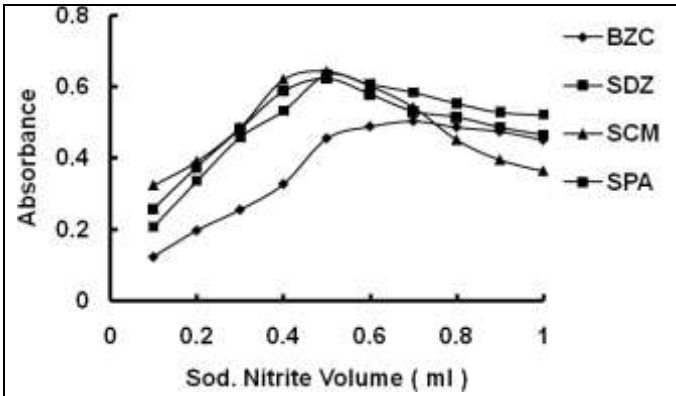


Figure (8): Effect of volume of nitrite on absorbance of the formed reaction product with Fenoterol

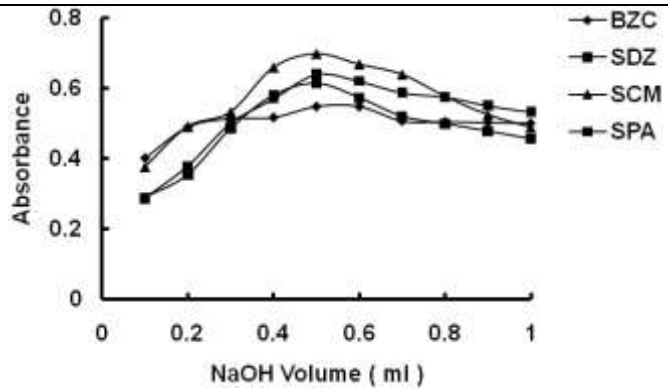


Figure (9): Effect of volume of NaOH on absorbance of the formed reaction product with Fenoterol

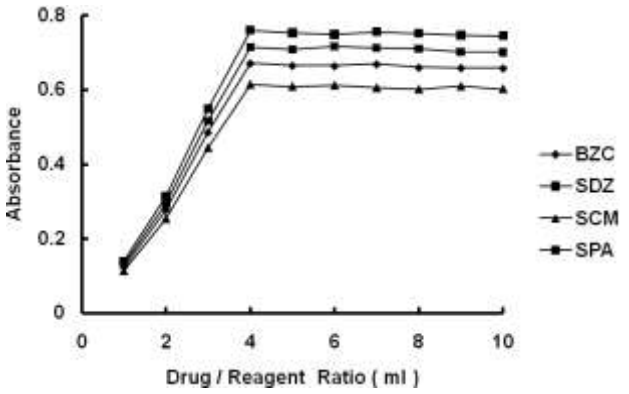


Figure (10): The stoichiometry of the reaction product of Fenoterol with diazotized BZC, SDZ, SCM and SPA by molar ratio.

Method B (Ion-pair with cobalt thiocyanat):

Fenoterol reacted with cobalt (II) thiocyanat to form stable ternary $[Co(SCN)_4]^{-2}$ complex which could be stabilized by forming ion-pair with similar compounds **(Shahine and Khamis, 1983; Cristina and Agustin,1985)**. This complex was sparingly soluble in aqueous solution, but readily extractable in organic solvents **(Shahine and Khamis, 1983)**. A high concentration of $[Co(SCN)_4]^{-2}$ was necessary for quantitative complexation, probably due to dissociation in aqueous medium of a fraction of the ion-pair formed **(Nerin *et al.*, 1985)**. It has been found that 4 ml of reagent were sufficient to give best results as shown in (figure 12). Ketones, especially methyl isobutyl ketones, alcohol and all oxygenated solvents, in general, could extract the cobalt (II) thiocyanat as well as its ternary complex **(Nerin *et al.*, 1985; Cristina and Agustin, 1985)**. Slightly polar or non-polar solvents, such as chloroform, methylene chloride, benzene and toluene, extracted only the ion-pair complex **(Cristina and Agustin, 1985)**. Toluene was found to be most convenient solvent as it gave the best results. A single extract of the ternary complex with toluene was sufficient for quantitative extraction. Second extraction gave a colorless organic solution. The blue ion-pair complex measured at λ_{max} 619 nm (figure 11) and was quite stable for several weeks. The composition of the complex in toluene extract was determined by molar ratio method it was 1:1 for drug : cobalt thiocyanate as shown in (figure 13). The regression equation, LOD, LOQ, response factor and A(1%, 1cm) were also recorded in table (1).

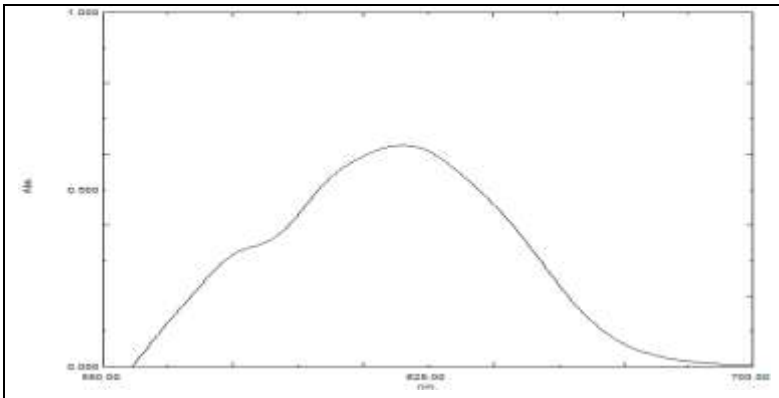


Figure (11): Absorption spectrum of Ion-pair complex formed by Fenoterol (50 $\mu g ml^{-1}$) with cobalt thiocyanate

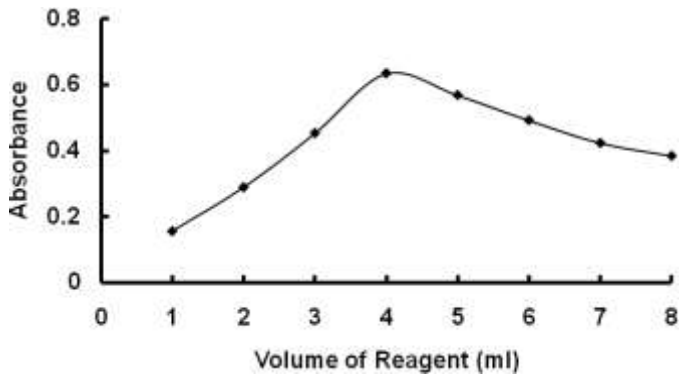


Figure (12) : Effect of $Co(SCN)_2$ volume on the absorbance of the reaction product with Fenoterol

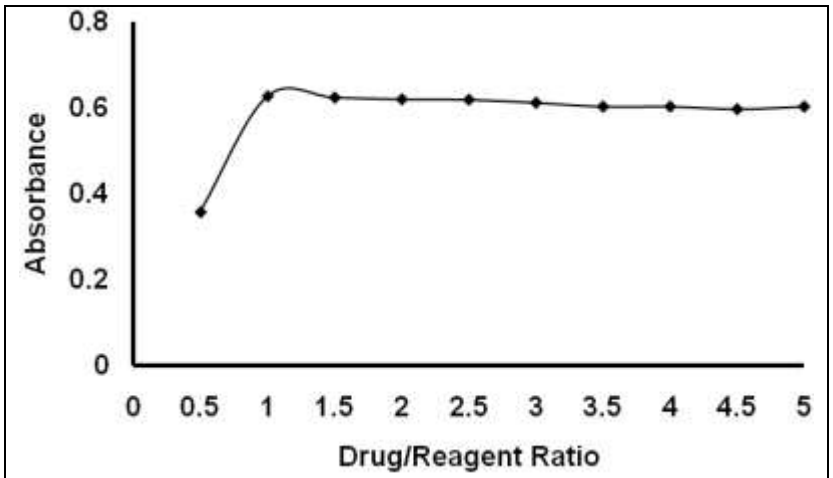


Figure (13): The stoichiometry of the reaction product of Fenoterol with $Co(SCN)_2$ by molar ratio.

Method C (Purssian blue technique):

Fenoterol reduce iron (III) to iron (II), the latter reacting with ferricyanide to form intense blue coloured Prussian blue **(Pesez and Bartos, 1965)** having an absorption maximum at 730 nm. (Figure 14). The optimum conditions were established by the use of 2 ml $FeCl_3$ (0.2%) as shown in (figure 15) and 2 ml pot. ferricyanide (0.2%), as shown in (figure 16). 1 ml of 10 M H_2SO_4 was found to give more stable colour and reproducible results compared to hydrochloric acid. It also found that the absorbance increase with time and reaches a maximum in 10 min. as shown in (figure 17) and remained stable for at least 4 hours. The regression equation, LOD, LOQ, response factor and A (1%, 1cm) were also recorded in table (1).

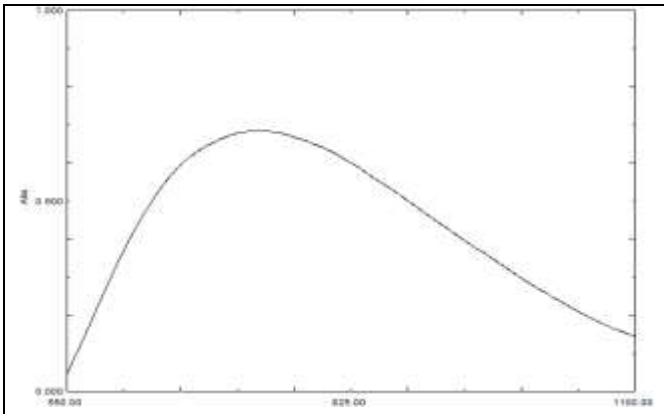


Figure (14): Absorption spectrum of Prussian blue formed by Fenoterol (7.5 μgml^{-1}) with ferric chloride and potassium ferricyanide.

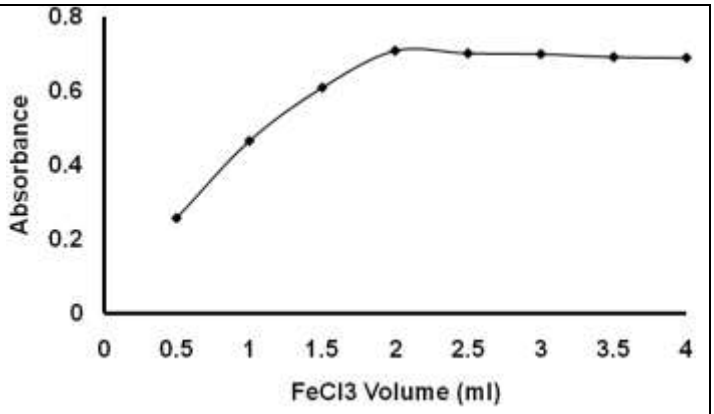


Figure (15): Effect of $FeCl_3$ volume on the absorbance of the reaction product with Fenoterol.

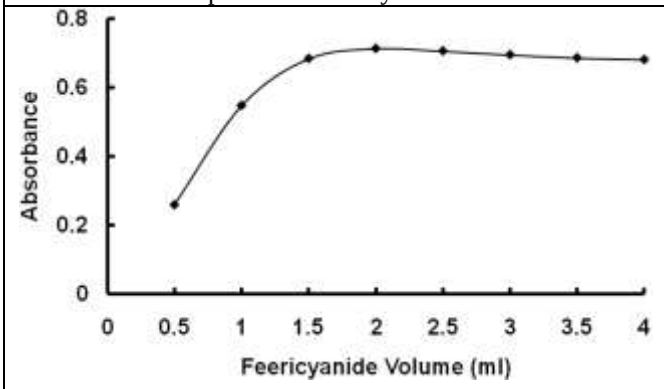


Figure (16): Effect of Ferricyanide volume on the absorbance of the reaction product with Fenoterol.

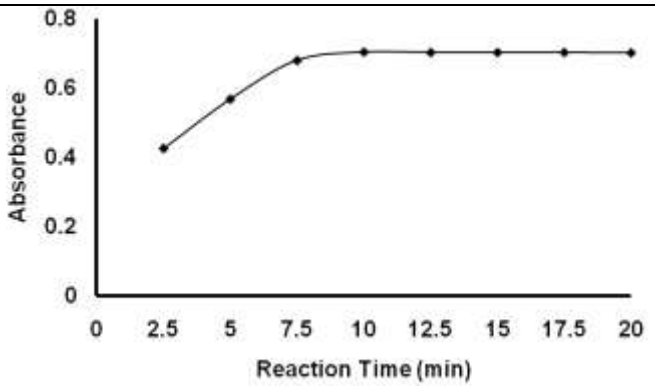


Figure (17): Effect of time on the absorbance of the reaction product of Fenoterol with $FeCl_3$/Ferricynide reagent.

Validation of the procedures :

Linearities :

The linearity range of the drug was validated, where good correlation between the absorbencies and the corresponding drug concentrations for method **A** in the range of 10-70, 6-42, 4-28 and 3.5-24.5μg ml^{-1}, with BZC, SDZ, SCM and SPA, respectively, for method **B** and **C** in the range of 10-70, 1.5–10.5 μg ml^{-1}, respectively.

LOD and LOQ:

The experimental LOD and LOQ for the described procedures were determined according to the USP **(United States Pharmacopeia, 2000)** Table (1).

Accuracy:

Accuracy was assessed by applying the standard addition technique as shown in tables (3,4).

Precision:

Intraday and interday precision of the proposed procedures were calculated, table (2) revealed the results of the developed methods.

Table (2): Intraday* and interday** accuracy and precision for the determination of Fenoterol by the proposed procedures:

Method		*Conc. µgml^{-1}*	*Intraday*			*Interday*		
			Found Conc. +SD	*Accuracy (R%)*	*Precision (RSD%)*	*Found Conc. ±SD*	*Accuracy (R%)*	*Precision (RSD%)*
A	**BZC**	40	40.05±0.211	100.12	0.297	40 ± 0.172	100	0.356
		50	49.93 ± 0.19	99.89	0.236	49.9 ± 0.056	99.80	0.441
		60	60 ± 0.002	100	0.320	59.5 ± 0.06	99.16	0.540
	SDZ	24	24.3 ± 0.031	101.25	0.236	24 ± 0.036	100	0.435
		30	29.9 ± 0.061	100.55	0.670	36.32 ±0.043	100.88	0.551
		36	36.2 ± 0.022	99.66	0.181	30 ± 0.061	100	0.281
	SCM	16	16.6 ± 0.051	100.37	0.213	16 ± 0.025	100	0.312
		20	19.9 ± 0.025	99.5	0.203	20 ± 0.046	100	0.196
		24	24.02±0.045	100.08	0.187	24.02 ± 0.045	100.08	0.342
	SPA	14	14.18±0.031	101.33	0.181	14 ± 0.062	100	0.281
		17.5	17.2 ± 0.002	98.5	0.297	17.23 ± 0.016	98.5	0.356
		21	21 ± 0.064	100	0.245	21 ± 0.102	100	0.437
B		40	40± 0.141	100	0.354	39.92± 0.056	99.8	0.144
		50	50.05±0.020	100.1	0.450	50± 0.032	100	0.435
		60	60.03±0.002	100.05	0.221	59.93± 0.003	99.88	0.134
C		4.5	4.48 ± 0.013	99.55	0.201	4.53 ± 0.071	100.66	0.351
		6	6.08 ± 0.002	101.30	0.532	6 ± 0.002	100	0.563
		7.5	7.5 ± 0.001	100	0.170	7.5 ± 0.002	100	0.171

* n = 4

** n = 3

Table (4): Application of standard addition technique for the determination of Fenoterol in its pharmaceutical preparation by Ion-pair, and Prussian blue techniques.

Method B			***Method C***		
Claimed taken (μgml^{-1})	Pure added (μgml^{-1})	Recovery* % of pure added	Claimed taken (μgml^{-1})	Pure added (μgml^{-1})	Recovery* % of pure added
20	20	99.2	3	3	100.16
	30	98.19		4.5	98.65
	40	99.3		6	99.10
	50	98.4		7.5	99.7
Mean ± SD		98.1 ±0.57			99.5 ±0.66
RSD%		0.57			0.66

* n = 5

Specificity:

Owing to the phenolic character of the drug investigated, the reaction was found to be specific for Fenoterol. It was also shown that excipients and diluents do not interfere with the proposed procedures.

Stability of standard solutions:

The stability of Fenoterol solution was evaluated by analysis of aqueous solutions of Fenoterol which was found to be stable for 7 days at room temperature and 3 weeks in refrigerator.

Analysis of pharmaceutical preparations:

The proposed procedures were also adopted for the determination of Fenoterol in Berotc® tablets. It should be pointed out that no interference by excipients and additives in Berotc® tablets. The recovery of the proposed methods was assured by applying the standard addition technique (Table 3, 4). The results obtained by the proposed procedures were statistically compared with those obtained by the reported spectrophotometric methods **(Negussie *et al.*, 2004)** after reaction with 4-aminoantipyrine. The data in Table 5 shows that the calculated "t" and "F" values are less than the tabulated ones, indicating no significant difference between the proposed methods and reported one, confirming accuracy and precision at 95% confidence limits.

Table (5): Statistical analysis of results obtained by the proposed and reported methods for the determination of Fenoterol in its pharmaceutical preparatio

Methods	*A*				*B*	*C*	Reported*** *Method*
	BZC	*SDZ*	*SCA*	*SPA*			
*N**	7	7	5	5	6	5	5
Mean	99.94	99.72	100.26	99.8	99.45	99.31	100.60
SD	1.26	0.29	1.4	0.62	0.62	0.62	0.77
RSD%	1.26	0.29	1.4	0.62	0.62	0.62	0.77
t**	0.76 (1.79)	0.80 (1.83)	0.70 (1.83)	0.24 (1.81)	1.29 (1.83)	1.97 (2.31)	
F**	1.29 (4.95)	1.42 (6.26)	1.06 (6.26)	1.9 (6.16)	2.01 (6.26)	2.37 (6.16)	

* Number of experimental.
** The values in parenthesis are tabulated values for "t" and "F" at $P < 0.05$.
*** The reported method involves spectrophotometric method (3)

CONCLUSION :

The proposed methods are simpler, faster, and more sensitive than the reported method.

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تعيين فينوتيرول بأستخدام ثلاث طرق طيف ضوئية مختلفة

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فى هذا البحث تم استنباط ثلاث طرق طيف ضوئية للتعيين الكمى لعقار فينوتيرول هيدروكلوريد سواء فى الصورته النقية أو المستحضر الصيدلى

الطريقة الأولى: تم استنباط طريقة لتعيين عقار فينوتيرول وذلك بترابطه كمادة فينولية مع ملح الديازونيوم المكون من أربع أمينات، بنزوكايين ، سلفاديازبين ، سلفاأسيتاميد وحمض سلفانيليك مكونا لونا أحمر "صبغة الآزو" يمكن قياسة ٥٢٦ ، ٥١٤ ، ٥١٢ و ٥١٣ ن.م على الترتيب وبتركيز يتراوح مابين ١٠ ـ ٧٠ ، ٦ ـ ٤٢ ، ٤ ـ ٢٨ ، 3.5 ـ 24.5ميكروجرام/مل على الترتيب للأربع كواشف.

الطريقة الثانية: تعتمد على تفاعل فينوتيرول مع مادة كوبلت كبريتوالسيانات حيث يتم تكون مركب أزرق شحيح الذوبان وهذا المركب يتم استخلاصه عن طريق التولوين كمذيب ويتم قياسه عند 619 ن.م وبتركيز يتراوح مابين ١٠ ـ 70 ميكروجرام / مل.

الطريقة الثالثة: تعتمد هذه الطريقة على أختزال الحديديك الى حديدوز عن طريق فينوتيرول فى وسط حمضى ثم يتم تفاعل الحديدوز مع سيانيد الحديديك لتكوين أزرق بروسيا له طول موجى 730 ن.م وبتركيز يتراوح مابين 1.5 – 10.5 ميكروجرام / مل.

هذا وقد تم تطبيق هذه الطرق بنجاح لتقييم عقار فينوتيرول كمادة خام وفى المستحضر الصيدلى كما تم مقارنة النتائج التى تم الحصول عليها بهذه الطرق بنتائج الطريقة المنشورة ووجد انه لاتوجد فروق تذكر بين نتائج تلك الطرق والطريقة المنشورة.