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SPECTROPHOTOMETRIC DETERMINATION OF MINOXIDIL IN PURE FORM AND ITS PHARMACEUTICAL PREPARATIONS

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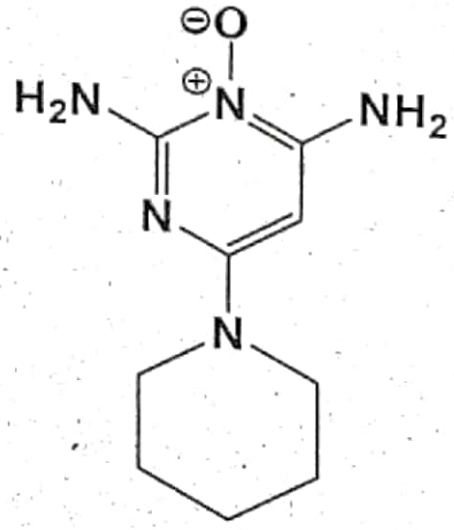
ABSTRACT

Four simple, accurate, sensitive and economical procedures (A-D) for the estimation of minoxidil, both in pure form and in pharmaceutical formulations have been developed. The first method (A) is based on the oxidation of the studied drug by a known excess of potassium permanganate in sulfuric acid medium directly ,followed by measuring the decrease in absorption of $KMnO_4$(A A method) at 525.6 nm. The second method (B) is based on the same principle with subsequent determination of unreacted potassium permanganate using methylene blue dye in the same acid medium at a suitable λ_{max} 664 nm . The third method is based on measuring manganate produced from the reaction of minoxidil with potassium permanganate in sodium hydroxide medium at λ_{max} 610 nm. While the fourth method is based on oxidation of the drug by Fe^{3+} in the presence of bipyridyl (bipy) in acetate buffer of pH 4.22 resulting in the formation of tris-complex which demonstrated λ_{max} at 530 nm. .Regression analysis of Beer-Lambert plots showed good correlations in the concentration ranges 8.0-40 , 2.0-20 and 2.0-10 μg ml^{-1} for methods A, B and C, D, respectively. Molar absorptivity and Sandell's sensitivity were calculated for each method . The optimum reaction conditions and other analytical parameters were evaluated. The proposed methods were applied to the determination of this drug in laboratory prepared tablets which contains the same contents of Loniten tablets , produced by (Pharmacia and Upjohn) .The influence of the substances commonly employed as excipients with this drug were studied. The suggested methods were compared with reference one , results have demonstrated that the methods are equally accurate and reproducible as the reference method.

INTRODUCTION

Minoxidil (6-(piperidin-1-yl)pyrimidine-2,4-diamine 3-oxide) is a peripheral vasodilator and it is used in scalp preparations for hair loss[1]. Various analytical techniques have been employed for the determination of minoxidil such as micellar electrokinetic capillary chromatography[2], narrow-bore LC/EC[3], capillary zone electrophoresis[4], ion-pair HPLC[5], capillary isotachophoresis[6], high-performance liquid chromatography with amperometric detection[7,8], reversed-phase HPLC[9], gas-chromatography[10], derivative spectrophotometry[11], Integrated flow injection-solid phase spectro-photometry[12], extractive spectrophotometric[13,14], spectrophotometry[15, 16, 17, 18, 19, 20], amperometric-FIA[21] and differential pulse polarography[22]. These techniques were used for minoxidil determination in biological fluids and pharmaceutical preparations.



Minoxidil

This work describes the development and application of simple and fast spectrophotometric procedures for the determination of minoxidil pure and in pharmaceutical formulations, with potassium permanganate in sulfuric acid medium at 525.6 nm. (Method A), with the previous reagent in presence of methylene blue at 664 nm. (Method B), with potassium permanganate in alkaline medium using 0.5 M sodium hydroxide at 610 nm. (Method C) and by the reaction of the cited drug with Fe^{3+}-bipy mixture in an acetate buffer medium of the optimum pH-value of 4.22 at 530 nm. (Method D).

EXPERIMENTAL

1- Apparatus:

SHIMADZU uv-1201 uv-vis spectrophotometer equipped with 10 mm quartez cell.

2- Materials and reagents:

All of the chemicals used were of analytical grade and all of the solutions were freshly prepared in distilled water.

(a) Pure minoxidil was obtained from Delta Pharm Company ,10th of Ramadane City.

Stock solution of minoxidil (200 μg ml^{-1}) was prepared by dissolving 20 mg of the drug in a small amount of acetic acid (about 5 ml) then completed to100 ml with distilled water.

(b) A stock solution of 5.0×10^{-3} M potassium permanganate (Aldrich) was prepared and standardized using sodium oxalate and stored in a dark bottle[23].

(c) Sulfuric acid ,2.0 M ; hydrochloric acid, 1M.

(d) An aqueous solution of methylene blue (MB) (Merck; 5.0×10^{-4} M) was prepared by dissolving the appropriate weight of the dye in a small volume of water , then making up to 100 ml in a calibrated flask. The solution of dye was allowed to stand at room temperature for about two weeks without any significant decay.

(e) Sodium hydroxide, 0.5 M.

(f) Iron(III)-bipyridyl[24]: prepared by dissolving 0.16 g of 2, 2'-bipyridyl (Fluka, Swiss) in 2 ml of 1 M HCl and 0.16 g of ferric ammonium sulfate dodecahydrate and diluted with distilled water to the mark in a 100 ml calibrated flask.

(g) Acetate buffer solutions; pH range from (3.5-6.0) were prepared by mixing appropriate quantities of 0.2 M sodium acetate with 0.2 M acetic acid to get the desired pH value[23].

(h) The following available Dosage forms were analyzed e.g.

- Performa spray, 5% minoxidil (Delta Pharm Company, 10th of Ramadan, Egypt).
- Rehair spray; 2% minoxidil (Adwic for pharmaceuticals and chemicals, Egypt).
- Laboratory prepared tablets similar to Loniten tablets , each tablet contains 2.5 mg, 5 mg or 10 mg minoxidil USP and lactose hydrous , microcrystalline cellulose , starch , colloidal silicon dioxide and magnesium stearate as excipients.

3- General procedure and calibration:

(a) ***Direct method using potassium permanganate, ΔA (method A):***

Into a 10-ml calibrated flasks, 0.4-2.0 ml aliquots (0.08-0.4 mg) of the sample solution (200 µg ml^{-1}) were transferred, followed by 2.5 ml of 2.0 M sulfuric acid and 1 ml of 5.0×10^{-3} M potassium permanganate solution. The flasks were shaken and allowed to stand for 5 minutes at room temperature and diluted with distilled water. The absorbance of a reagent blank was measured against the experiment at 525.6 nm . The concentration of the drug was determined from a calibration graph constructed under the same conditions.

(b) ***Indirect method ,using potassium permanganate and methylene blue dye (method B):***

Into a 10-ml calibrated flasks, 0.1-1.0 ml aliquots (0.02-0.2 mg) of the sample solution (200 µg ml^{-1}) were transferred in a series, followed by acidification using 2.5 ml of 2.0 M sulphuric acid , 1.0 ml of 5.0×10^{-3} M potassium permanganate and 2.0 ml of 5.0×10^{-4} M methylene blue solutions were added and the flasks were shaked and allowed to stand for 5 minutes at room temperature. The volume was completed in each flask to 10 ml with water. Absorbance of methylene blue was measured spectrophotometrically at 664 nm against a reagent blank omitting the drug (table 1). The concentration of the drug was determined from a calibration graph constructed under the same conditions.

(c) ***Method C, using (potassium permanganate and sodium hydroxide):***

Into a 10-ml calibrated flasks, 0.1-0.5 ml aliquots (0.02-0.1 mg) of the sample solution (200 µg ml^{-1}) were transferred in a series, followed by 1.0 ml of 5.0×10^{-3} M potassium permanganate and 1.5 ml of 0.5 M sodium hydroxide solutions the reaction mixture was left for 5 minutes at room temperature. Absorbance was measured at 610 nm against a reagent blank omitting the drug after dilution to volume with distilled water , The concentration of the drug was determined from a calibration graph constructed under the same conditions (table 1).

(d) ***Method D, using (Fe^{3+}-Bipyridyl reagent):***

Into a 10-ml calibrated flasks, 0.1-0.5 ml aliquots (0.02-0.1 mg) of the sample solution (200 µg ml^{-1}) were transferred in a series, followed by 3.0 ml of Fe^{3+}-bipy reagent solution and 3 ml acetate buffer solution , pH 4.22 .The mixture was heated on a water bath at about 80° C for 15 min. , then cooled to room temperature (25 ± 1° C) , then the volume was completed to the mark with distilled water. The developed color was measured at 530 nm against a reagent blank treated similarly. The concentration of drug was determined from a calibration graph constructed under the same conditions.

4- Procedure for pharmaceutical formulations:

(a) ***Procedure for laboratory prepared tablets containing the same contents of Loniten tablets:***

The contents of 10 laboratory prepared tablets , containing 10 mg of minoxidil drug in each one was powdered and mixed . Accurately weighed amount of the powder equivalent to 20 mg of minoxidil was dissolved in about 5 ml of acetic acid and 50 ml of distilled water, shaken and filtered, washed with water. The clear filtrate was diluted to 100 ml with water in 100 ml measuring flask. The proper volumes of the solution were pipetted into a series of 10 ml volumetric flasks , Then follow the same procedures described for determination of minoxidil as in authentic sample in general procedure A ,B and D. For procedure C, the weight equivalent to 20 mg minoxidil was shaken and dissolved in 80 ml methanol ,filtered in 100 ml volumetric flask ,washed and completed to the mark with the same solvent. The methanolic solution was evaporated under vacuum till dryness .then the residue which contains the drug was dissolved in 5% acetic acid. Then follow the same procedure described for determination as in authentic sample in general procedure C.

RESULTS AND DISCUSSION

1. Absorption spectrum:

i- ***Methods A and B:***

The spectrophotometric method for the determination of minoxidil is based on their oxidation with known excess of potassium permanganate in acidic medium directly and subsequent measuring the decrease in the absorbance of added potassium permanganate, ΔA (method A) or by subsequent determination of residual oxidant by reacting it with fixed amount of methylene blue , (method B) . In method A the absorbance of $KMnO_4$ at 525.6 nm, was measured against the experiment (ΔA) (figure 1). But in method B the absorption spectrum of methylene blue was measured against a blank experiment carried out similarly at 664 nm (figure 2) left after the reaction between the cited drug , potassium permanganate and methylene blue.

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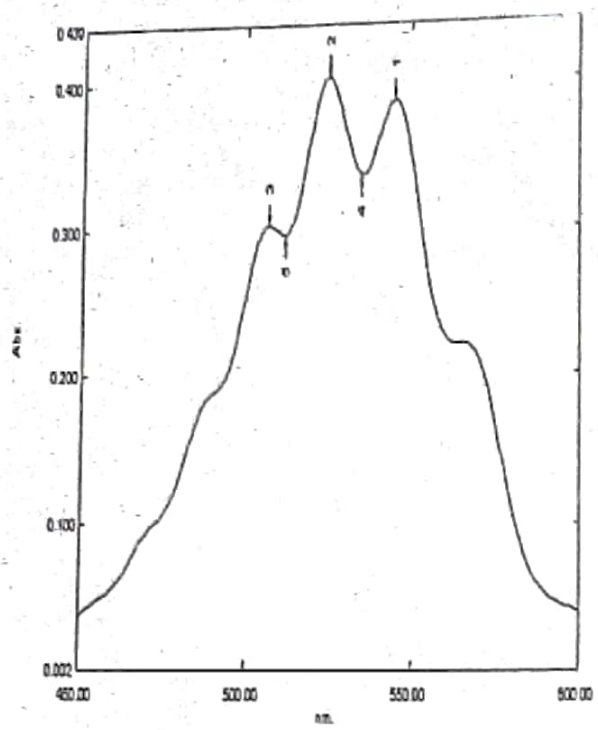


Figure (1): Absorption spectrum of the reaction between 20 µg ml^{-1} minoxidil and 1 ml 5.0×10^{-3} M $KMnO_4$ in 2.5 ml 2 M sulfuric acid medium ($KMnO_4$ spectrum)

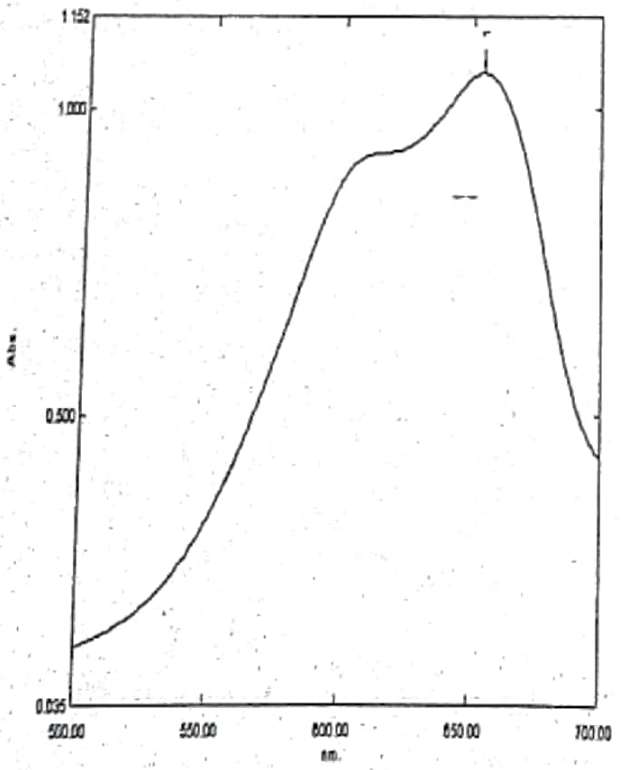


Figure (2): Absorption spectrum of the reaction between 20 µg ml^{-1} minoxidil 1 ml 5.0×10^{-3} M $KMnO_4$ in 2M sulfuric acid medium, 2.5 ml and 2 ml 5.0×10^{-4} M methylene blue dye (methylene blue spectrum).

Optimization of the analytical procedures:

1. *Effect of time:*

In order to obtain the highest and most stable absorbance, the effect of time on the oxidation reaction was studied. The reactions were performed at room temperature 25± 2°C for the periods ranging from 3-20 min. Maximum and constant absorbance was obtained after 5 min for methods A and B.

2. *Effect of oxidant concentration:*

When studying the effect of potassium permanganate referring to decrease in its color intensity (method A) and increasing of methylene blue color intensity (method B), it was observed that , in both cases the absorbance reached maximum when 1.0 ml of 5.0×10^{-3} M potassium permanganate solution was added to a total volume of 10 ml. Therefore, 1.0 ml of potassium permanganate was used for all measurements of methods A and B and in case of method B, 2ml of 5.0×10^{-4} M methylene blue was sufficient when added to the mentioned volume of 5.0×10^{-3} M $KMnO_4$ to give maximum absorbance.

3. *Effect of acidity:*

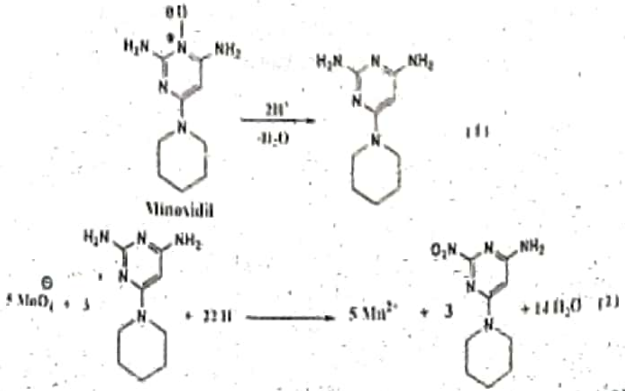
To study the effect of sulfuric acid concentration , the reaction was performed in a series of 10 ml volumetric flasks containing different volumes (0.5-5.0 ml) of 2.0 M sulfuric acid and 1.0 ml of potassium permanganate. It was found that the maximum absorbance was obtained at 2.5 ml of 2.0 M sulfuric acid, beyond which the absorbance slightly decreases. Thus 2.5 ml of 2.0 M sulfuric acid was used throughout the experiment.

4. *Effect of dye concentration:*

In order to ascertain the linear relationship between the volume of added minoxidil and the decrease in absorbance of methylene blue, experiments were performed in 2.5 ml of 2.0 M sulfuric acid ,1ml 5.0×10^{-3} M KMnO4 and different volumes of methylene blue . It was found that 2.0 ml of methylene blue gave maximum absorbance at 664 nm (table 1) and the absorbance of methylene blue was directly proportional with the concentrations of minoxidil and the color was stable up to 24 hours.

5. *Chemistry of oxidation products:*

The proposed methods are based on the oxidation of the cited drug by excess of $KMnO_4$ (method A), followed by the estimation of unreacted $KMnO_4$ using methylene blue (method B), the possible sequence of reaction with $KMnO_4$ was presented in this scheme.



The stoichiometric coefficient of the reaction between minoxidil and $KMnO_4$ is 1.7, corresponding to 5 $KMnO_4$:3 minoxidil. On the basis of this stoichiometric ratio, a suggested redox reaction is proposed (equations 1 and 2) indicating that the N → O bond is decomposed in acid media[25].

ii- *Method C:*

The reaction between the selected drug and KMnO4 in alkaline medium of sodium hydroxide yields a greenish blue color due to formation of manganate ions (MnO_4^{-2}) exhibiting maximum absorption at 610 nm (figure 3). Primary and secondary amines were reported to be oxidized by $KMnO_4$ giving different products depending on the nature of alkyl group (R)[26].

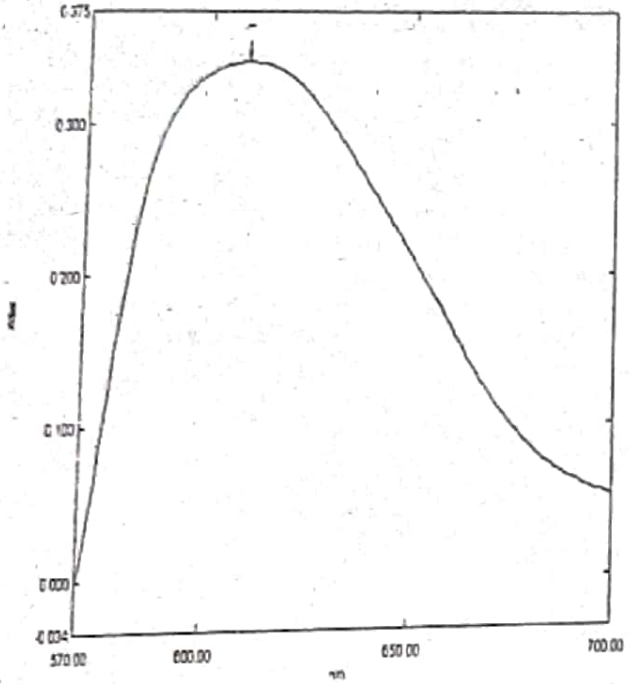


Figure (3): Absorption spectrum of the reaction product between 6 μg ml^{-1} minoxidil and 1ml 5.0×10^{-4} M $KMnO_4$ in 0.5M sodium hydroxide medium

Investigations of method C parameters:

a- *Effect of time:*

The optimum time for analysis of minoxidil using $KMnO_4$ in alkaline medium was 5 minutes and the color was stable for at least 30 minutes.

b- *Effect of* $KMnO_4$ and sodium hydroxide reagent:

The optimum volume which gave maximum color intensity at 610 nm was 1 ml 5.0×10^{-3} M $KMnO_4$ and 1.5 ml of 0.5 M sodium hydroxide.

iii- *Method D:*

2,2'-bipyridyl is organic base and chelates the iron (III). This method was based on the formation of tris(2,2'-bipyridyl)-iron (II) chelate upon the reaction of minoxidil with Fe^{3+}-bipy reagent. The reaction proceeds through the reduction of Fe^{3+} to Fe^{2+} by minoxidil and subsequent formation of an intensive orange-red coloration of the chelate[24]. The absorption spectrum of the colored chelate species in the proposed method at the optimum conditions was scanned against a reagent blank in the range 400- 600 nm and recorded in the general procedures to show a characteristic λ_{max} at 530 nm (figure 4).

The experimental conditions were established by varying each parameter individually and observing its effect on the absorbance of the colored species. All the spectral characteristics and the measured or calculated parameters are summarized in table 1.

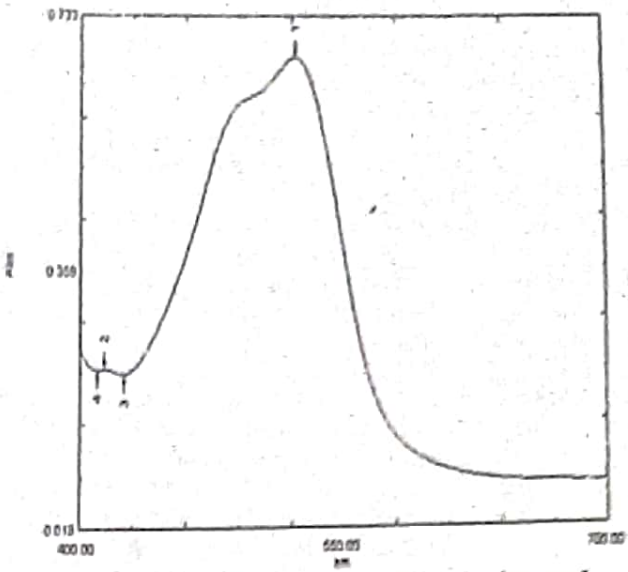


Figure (4): Absorption spectrum of the reaction product between 5 μg ml^{-1} minoxidil and Fe^{3+}-bipyridyl reagent in acetate buffer of pH 4.22

Optimization of the experimental conditions of method D:

1. *Effect of pH:*

Acetate buffer solution of different pH values were studied. The optimum pH value was 4.22. The pH adjustment is necessary especially in acidic medium because the reaction was affected by the change of the pH in the range of (2.5-6.5). Moreover, 3.0 ml of a buffer solution was sufficient for complete color development.

2. *Effect of reagent concentration:*

The addition of 3.0 ml of Fe^{3+}-bipy reagent was sufficient to obtain the maximum and reproducible absorbance, smaller amounts give incomplete chelate formation. Whereas a larger concentration had no effect on chelate formation due to the background of the reagent used, although the absorbance increased slightly.

3. *Effect of temperature and heating time:*

The effect of temperature and heating time on the formation of the colored chelate were studied. The reaction of minoxidil with 2,2'-bipyridyl-Fe^{3+} proceeds very slowly at room temperature. Higher temperature was used to accelerate the reaction. Maximum absorbance was obtained after heating for about 15 min with Fe^{3+}-bipy in a water bath at about 80°C. Further, heating caused no appreciable change in the color. The obtained chelate was very stable for more than 10 hours.

2. Interferences:

The effects of various excipients were investigated on the determination of minoxidil in dosage forms. Results indicated that various excipients interfere with the assay of the drug mentioned above in topical pharmaceutical preparations e.g. Rehire and Performa preparations where these preparations containing propylene glycol which is oxidized by $KMnO_4$ giving pyruvic acid ,but upon application of the proposed methods to the determination of the cited drug in the laboratory prepared tablets which contains

the same contents (lactose hydrous, microcrystalline cellulose, starch, colloidal silicon dioxide and magnesium stearate and 10 mg minoxidil) of Loniten tablets produced by: Pharmacia and Upjohn, give accurate and reproducible results as the reference one.

3. **Analytical data:**

(a) *Linearity:*

Under the above mentioned experimental conditions, standard calibration graphs were constructed for the determination of minoxidil with the proposed methods. Beer's law was obeyed for drug analyzed in concentrations range of 8.0-40, 2.0-20 and 2.0-10 µg ml^{-1} with methods A, B and C or D respectively as presented in table 1. The linear regression equations, slopes, intercepts, correlation coefficients, standard deviation, relative standard deviation. The molar absorptivities and linearity ranges were calculated and given in (tables 1 and 2) for each proposed method.

(b) *Accuracy and precision:*

In order to determine the accuracy and precision of the proposed methods, solutions containing four different concentrations of minoxidil were prepared and analyzed in six replicates. The relative standard deviation to assess precision and percentage relative error (Er %) to assess accuracy of the suggested method, were calculated at 95% confidence level to be considered satisfactory. The percentage relative error calculated using the following equation:

Er % = [(found – added) / added] x 100

The inter-day and intra-day precision and accuracy results are shown in table (3). It shows that the proposed methods have good repeatability and reproducibility.

4. **Analytical applications:**

The proposed methods were successfully used for determination of minoxidil in raw material (table 2) and in tablets dosage form (table 1) and not used for topical formulations which contain propylene glycol beside the studied drug. The performance of the proposed methods was assessed by calculation of the t-test (for accuracy) and a variance ratio F-value (for precision) compared with the reference (uv) method[27] for 95% confidence level with five degrees of freedom[27]. The results showed that the t- and F-values were less than the critical value, indicated that there was no significant difference between the proposed and reference method as shown in table (5). The proposed methods were precise, reproducible and with high recovery percentages ,so they can be recommended for the routine analysis of minoxidil in drug quality control laboratories.

Table (1): Analytical parameters and optical characteristics of the proposed methods with minoxidil

Parameters	A	B	C	D
Media	H_2SO_4 (2 M)	H_2SO_4 (2 M)	NaOH (0.5 M)	pH (4.22)
Volume of the used media	2.5	2.5	1.5	3
Volume of the reagents used.	1ml $KMnO_4$	1 ml $KMnO_4$+2ml M.B.	1 ml $KMnO_4$+1.5ml NaOH (0.5 M)	3.0 ml of Fe^{3+}-bipy+3ml acetate buffer
λ_{max}, nm	525.6	664	610	530
Beer's law limits µg/ml	8-40	2-20	2-10	2-10
Molar absorptivity x 10^{-4} (L mol^{-1} cm^{-1})	0.3138	1.2659	1.1548	2.9833
Sandell sensitivity	2.042×10^{-3}	6.043×10^{-3}	5.513×10^{-3}	14×10^{-3}
Regression equation *				
Slope (b)	0.0259	0.05498	0.05295	0.1053
Intercept (a)	-0.0828	0.03154	0.0097	0.1621
Correlation coefficient (r)	0.9999	0.9999	0.9999	0.9999
± SD	0.598	1.005	0.514	0.835
± SE	0.268	0.410	0.230	0.374
± RSD	0.597	1.01	0.514	0.834
±RE%	0.653	0.453	0.563	0.913
Confidence limit	99.85 -100.43	99.27-100.07	99.72 -100.22	99.69-100.51

* C = A-a /b, where C = concentration of the drug in µg ml^{-1}, A absorbance of the reactions product, a= intercept and b= slope

Table (2): Results of the analysis for determination of minoxidil authentic sample using proposed methods

	A		B			C	D
	Taken $\mu g\ ml^{-1}$	Recovery* %	Taken $\mu g\ ml^{-1}$	Recovery* %	Taken $\mu g\ ml^{-1}$	Recovery* %	Recovery* %
	8.0	99.13	2.0	98.50	2.0	99.50	101.00
	10.0	99.17	4.0	98.50	4.0	99.75	100.50
	20.0	100.13	8.0	100.63	6.0	100.83	99.00
	30.0	99.14	12.0	100.83	8.0	99.75	99.50
	40.0	101.43	16.0	99.88	10.0	100.00	100.50
	-	-	20.0	99.70	-	-	-
Mean	100.14		99.67			99.97	100.10
N	5		6			5	5
Variance	0.358		1.01			0.265	0.698
±SD	0.598		1.005			0.514	0.835
±SE	0.268		0.410			0.230	0.374
±RSD	0.597		1.01			0.514	0.834

*Average of three determinations

Table (3): Evaluation of accuracy and precision data for minoxidil analysis by the proposed methods

Method	Intra-day				Inter-day		
	Added (μgml^{-1})	Recovery %	Precision RSD % [a]	Accuracy Er %	Recovery %	Precision RSD % [a]	Accuracy Er %
A	8.0	98.64	0.983	-1.375	99.40	0.936	-0.396
	16.0	100.19	0.795	+0.563	100.11	0.416	+0.104
	30.0	99.59	0.404	-0.494	99.56	0.348	-0.444
	40.0	101.28	0.359	+1.279	101.25	0.157	+0.879
B	4.0	99.42	0.773	-0.583	99.63	0.905	-0.375
	8.0	100.30	0.515	+0.292	100.63	0.480	+0.479
	12.0	100.71	0.680	+0.708	100.06	0.525	+0.056
	16.0	99.96	0.387	-0.042	99.72	0.442	-0.281
C	4.0	101.08	1.267	+1.08	99.58	0.606	-0.417
	6.0	101.00	0.616	+1.00	100.11	0.713	+0.11
	8.0	99.86	0.432	+0.063	99.79	0.285	-0.208
	10.0	100.10	0.558	+0.10	99.77	0.367	-0.233
D	2.0	99.75	1.297	0.083	99.67	0.683	-0.333
	4.0	99.58	0.668	-0.417	99.75	0.592	+1.25
	6.0	99.53	0.683	-0.472	99.50	0.647	-0.50
	8.0	99.44	0.915	-0.563	99.71	0.724	-0.292

RSD%: percentage relative standard deviation, Er%, percentage relative error
[a]Mean of six determination.

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Table (4): Determination of minoxidil in laboratory prepared tablets (similar to Loniten tablets, containing 10 mg minoxidil) using the proposed methods

	A		B		Taken µg ml^{-1}	C	D
	Taken µg ml^{-1}	Recovery* %	Taken µg ml^{-1}	Recovery* %		Recovery* %	Recovery* %
	10.0	98.80	4.0	99.30	2.0	98.50	99.50
	16.0	98.88	8.0	99.00	4.0	99.25	99.75
	24.0	100.33	12.0	100.88	6.0	100.83	99.83
	32.0	99.63	16.0	101.17	8.0	100.13	99.88
	40.0	99.80	18.0	100.06	10.0	99.60	98.60
Mean	99.49		100.12			99.66	99.31
N	5		5			5	5
Variance	0.417		0.831			0.777	0.322
± SD	0.646		0.911			0.881	0.567
± SE	0.289		0.407			0.394	0.254

*Average of three determinations

Table (5): Statistical analysis of results obtained by the proposed methods applied on pure and laboratory prepared tablets (similar to Loniten tablets)

Sample		Reference method	Proposed methods			
			A	B	C	D
Minoxidil pure	X^{a} ±SD	100.06 ± 0.771	100.14 ±0.598	99.67± 1.005	99.97±0.514	100.10 ±0.835
	t^{b}		0.046	0.914	0.458	0.118
	F^{c}		1.66	1.700	2.242	1.175
Laboratory prepared tablets	X^{a} ±SD	99.92 ± 0.508	99.49 ± 0.646	100.12 ± 0.911	99.66 ± 0.885	99.31 ± 0.567
	t^{b}		1.17	0.428	0.571	0.268
	F^{c}		1.62	3.22	3.012	1.25

*Average of three determinations
^{b}Calculated t-value; tabulated t-value for five degrees of freedom, and p= 0.05 is 2.57
^{c}Calculated F-value; tabulated F-value for five degree of freedom, and p= 0.05 is 5.05

CONCLUSION

The proposed methods is simpler, less time consuming and more sensitive than most of the reported methods (2-22), where they are non extractive not expensive, do not require modern apparatus and the spectrophotometric methods for minoxidil analysis are few in number as indicated in the literature so they are advantageous over some of other reported methods and can be used in drug quality control laboratories.

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طرق طيفية لتعيين عقار المينوكسيديل خام وفى المستحضرات الصيدلية المحتوية عليه

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لقد تم استنباط أربع طرق بسيطة و دقيقة و حساسة لتعيين عقار المينوكسيديل خام وفى المستحضرات الصيدلية المحتوية علية (بيرفورما) مستحضر لعلاج الشعر و أقراص محضرة بالمعمل تحتوى على العقار والمواد المضافة له (مثل أقراص لونيتين المصنعة بايطاليا) وتستخدم لعلاج الضغط . *وتعتمد الطريقة الأولى* على تفاعل العقار مع كمية كبيرة ومحسوبة من برمنجنات البوتاسيوم وقياس النقص في لون برمنجنات البوتاسيوم عند طول موجى 525.6 نانوميتر *وتعتمد الطريقة الثانية* على نفس أساسيات الطريقة الأولى مع إضافة كمية ثابتة من صبغة المثيل الأزرق لكي تتفاعل مع البرمنجنات الغير متفاعلة مع العقار وقياس لون الصبغة عند طول موجى 610 نانوميتر *وتعتمد الطريقة الثالثة* على تفاعل العقار مع برمنجنات البوتاسيوم فى وسط قاعدي باستخدام فيدروكسيد الصوديوم(5 .0 مولار) مكونة منجانات البوتاسيوم ذات لون أزرق مخضر يقاس عند طول موجي (610) نانومتر *وتعتمد الطريقة الرابعة* على أكسدة العقار باستخدام حمض [illegible] والبايبريدين وقياس ناتج التفاعل عند طول موجي 530نانومتر وقد تم تعيين العقار بنجاح للتركيزات من 2- 10 ميكروجرام لكل مل وقد تم أيضا دراسة العوامل المؤثرة على التفاعل بالطرق المختلفة المذكورة حتى تم التوصل الى أحسن نتائج وقد تم تطبيق الطرق المقترحة لتعيين العقار فى المستحضرات الصيدلية المحتوية علية (بيرفورما) مستحضر لعلاج الشعر و أقراص مثل أقراص لونيتين المستخدمة لعلاج الضغط . وقد تبين أن الطرق المقترحة تستخدم بنجاح للأقراص فقط ولا تستخدم للبيرفورما لوجود مواد تتداخل فى التفاعل مثل البر وبيلين جليكول . وقد تم مقارنة الطرق المقترحة بطريقة مرجعية ووجد أنها متساوية لهم في الدقة لذا يوصى باستخدام الطرق المقترحة لتحليل العقار كمادة خام وفى الأقراص المحتوية عليه.