Asian Journal of Chemistry Vol. 20, No. 5 (2008), 3585-3590

Ion-Pair Extraction-Spectrophotometric Determination of Trace Amounts of Minoxidil

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A simple, sensitive and selective extraction-spectrophotometric method for the determination of trace amounts of minoxidil is reported. The minoxidil-orange-II ion pair in acidic media is quantitatively extracted into dichloromethane and its absorbance is measured at 482 nm at room temperature. The effect of different variables such as solvent, volume of extracting solvent, volume of anionic reagent, pH, ionic strength (NaCl 0.1 M) and shaking time is investigated and optimum conditions for quantitative extraction of minoxidil is obtained. Calibration graph is linear over the minoxidil concentration range of 0.3-6.0 μg mL^{-1} and a regression coefficient of 0.9974 is obtained. The relative standard deviation of 8 replicate determination of 3.0 μg mL^{-1} of minoxidil is 3.54 %. Limit of detection of the method is 43.2 ng mL^{-1}. The method is used for determination of minoxidil in 5 % solution and also mixture solution of minoxidil and tertinoin and good results are obtained.

Key Words: Minoxidil, Extraction, Orange II, Determination.

INTRODUCTION

Minoxidil (MX) (Fig. 1) is a very efficacious orally active vasodilator. Like hydralazine, it dilates arterioles but not veins. Because of its greater potential antihypertensive effect, fluoxetine should replace hydralazine when maximal doses of the later are not effective or in patients with renal failure and severe hypertension, who do not respond well to hydralazine. Minoxidil must be used in combination with a β-blocker and a loop diuretic. Tachycardia, palpitations, angina and edema are observed when doses of β-blockers and diuretics are inadequate. Minoxidil is a well absorbed from gastrointestinal tract and is metabolized, primarily by the glucuronide conjugation, in the liver. Minoxidil is not protein-bound and its half-life average is 4 h[1-4]. Various analytical techniques have been reported for the determination

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of minoxidil including capillary isotacho-phoresis[5], derivative spectrophotometry[6] and differential-pulse polarography[7]. These methods are either insensitive or inconvenient for topical formulation development with minoxidil. A scintillation counting[8] using radiolabeled minoxidil formulation is very sensitive and is widely used in the pharmaceutical industry for minoxidil formulation development.

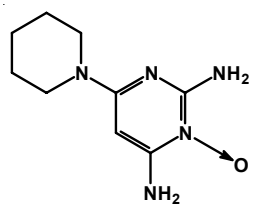

Fig. 1. Structure of minoxidil

Solvent extraction is perhaps the most versatile of analytical techniques, in that it has an extremely wide range of application and invokes most of the physical and chemical principles used generally in analytical chemistry[9-11]. It therefore has pedagogic as well as practical value. Extraction methods using ions associated with a large ionic dye or counter ions, forming an ion-association complex with large molar absorptivities are still limited[12,13]. Many quantitative pharmaceutical determination methods such as HPLC suffer from large solvent consumption[14-20]. More investigation in this field could lead to sensitive methods for trace pharmaceutical determinations.

This paper describes a simple and sensitive method for the quantitative extraction of MinoxidilH^+-orange-II^- ion pair from an acidic solution into dichloromethane organic solvent followed by spectrophotometric measurements at 482 nm.

EXPERIMENTAL

All the chemicals were of the highest purity available and used without further purification. Double distilled deionized water was used throughout.

100 μg mL^{-1} stock solution of minoxidil (purchased from minoxidil, 99.9 % pure) was prepared by dissolving 0.0500 g of minoxidil powder in water and diluting to the mark in a 500 mL volumetric flask with distilled water. Working solutions were prepared by appropriate dilution of the stock solution with water.

Orange II (OR), stock solution (8.0×10^{-4} M) was prepared by dissolving proper amount of the dyestuff (Merck) in water and diluting to the mark in a 500 mL volumetric flask.

0.01 M solution of hydrochloric acid was prepared by diluting 0.50 mL of the concentrated acid to 500 mL in a volumetric flask.

The absorption spectra were recorded on a Jasco Model 7850 UV-Vis recording spectrophotometer and a Perkin-Elmer model 550S spectrophotometer was used for absorbance measurements. All pH measurements were made by a Metrohm digital pH meter equipped with a combined glass electrode.

Recommended procedure: An aliquot of sample solution containing 0.1-8.0 µg of minoxidil was placed in a 10 mL volumetric flask. 2.0 mL of orange-II solution (8.0×10^{-4} M), 0.5 mL of 0.01 M of HCl solution and 2.0 mL of 0.1 M of NaCl solution were added and the solution was diluted to the mark with distilled water. The solution was transferred into a 50 mL separatory funnel and 4 mL of dichloromethane was added. The solution was shaken vigorously for 1 min. The phases were allowed to separate and the organic phase was separated and its absorbance was measured at 482 nm against a reagent blank.

RESULTS AND DISCUSSION

Since minoxidilH^+ cation forms a fairly stable ion-pair with orange-II anionic dyestuff as counter ion in aqueous acidic solution, it is expected to result in a sensitive and useful spectroscopic method for trace minoxidil determination.

In preliminary experiments it was found that the counter anion plays an important role in the formation of a stable ion-pair and among the dyestuffs examined such as methyl green, brilliant green, thionine, nile blue, methylene blue, safranine and orange-II (OR), best results were obtained with orange-II dyestuff.

Choice of organic solvent: The extraction process was performed with some common organic solvents such as dichloromethane, chloroform, carbon tetrachloride, methyl isobutyl ketone and benzene. It was found that the ion-pair is readily extractable in dichloromethane, while in other solvents used, the coloured complex could not be extracted into the organic phase as completely as dichloromethane.

Effect of orange-II concentration: The effect of orange-II concentration on the extraction of minoxidilH^+-OR^- ion-pair was investigated and the results are shown in Fig. 2. It is seen that the absorbance of the organic phase increases with increasing orange-II concentration in the aqueous phase. The concentration 2.0×10^{-5} M of orange-II in the final solution was chosen as the optimum concentration of orange-II.

Effect of HCl concentration: The effect of acidity of the test solution on the extraction process of minoxidilH^+-OR^- ion-pair was studied using hydrochloric acid (0.01 M) solutions. On the basis of the results presented in Table-1, 0.5 mL of hydrochloric acid (0.01 M) solution gives the best results.

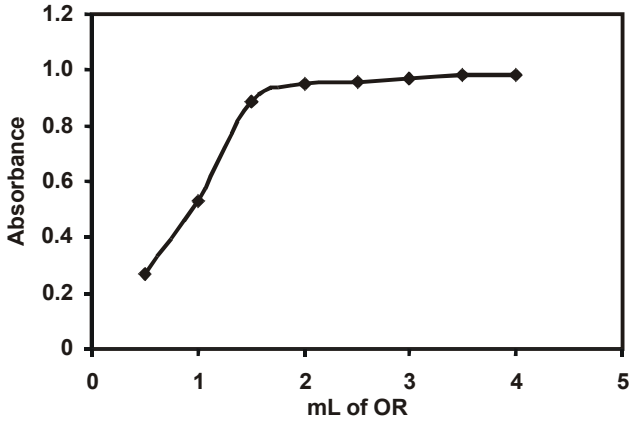

Fig. 2. Effect of OR concentration on the absorbance of extracted minoxidilH^+-OR^- ion-pair

TABLE-1
EFFECT OF HCl CONCENTRATION ON THE EXTRACTION OF MINOXIDIL H^+-OR^- ION-PAIR

mL of HCl solution	Absorbance of extracted ion-pair	mL of HCl solution	Absorbance of extracted ion-pair
0.1	0.23	0.5	0.82
0.2	0.40	0.6	0.81
0.3	0.59	0.7	0.82
0.4	0.77	0.8	0.82

Effect of solvent volume: It must be mentioned that quantitative extraction of minoxidilH^+-OR^- ion-pair is complete by 4 mL of dichloromethane in a single stage extraction process. This was confirmed by observing further enhancement in the absorption of complex in the mixture of two 4 mL portions of the organic phase obtained from two successive extraction of an aqueous minoxidilH^+-OR^- ion-pair solution, compared with that of an 8 mL organic phase obtained from a single stage extraction of the same complex solution under optimal experimental conditions. The absorbance reading for 8 mL organic phase containing the minoxidilH^+-OR^- ion-pair is half of the absorbance from 4 mL dichloromethane from the first stage of extraction.

Effect of shaking time: The effect of shaking time on the extraction of minoxidilH^+-OR^- ion-pair was studied. A shaking time of 30 s was found to be sufficient for the extraction of ion-pair. By increasing the shaking time, the absorbance of related blank will increase and absorbance decreases.

Analytical performance: Under the optimum conditions described above, linear calibration graph for minoxidil was obtained in the concentration range of 0.3-6.0 μg mL^{-1}. The regression equation for minoxidil is $A_{minoxidil} = 0.058\ C_{minoxidil} + 0.021$ (where $A_{minoxidil}$ is the absorbance of the sample against a blank solutions and $C_{minoxidil}$ is the concentration of minoxidil in μg mL^{-1}) with a correlation coefficient of 0.9974. The relative standard deviation (RSD) of ten replicate determinations of 5.0 and 1.0 mg mL^{-1} of minoxidil are 2.16 and 3.76 %, respectively and the limit of detection (LOD)[21] of the method is 43 ng mL^{-1}.

Effect of interferences: In order to study the influence of various cations and anions on the determination of minoxidil, a fixed concentration of minoxidil, 5.0 μg mL^{-1}, was taken with different amounts of foreign ions and the recommended procedure was followed. A relative error of ± 3 % with respect to the absorbance difference for the minoxidil solution was considered tolerable. Tolerance limits are as follows: Cl^-, NO_3^-, Na^+ (10000 folds); SO_4^{2-}, Ca^{2+}, Ba^{2+}, Sr^{2+}, Mg^{2+}, K^+, Li^+, Zn^{2+}, Cd^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Mn^{2+}, NH_4^+, Cr^{3+} (200 folds); Br^-, I^-, CH_3COO^-, ClO_3^- (100 folds); Hg^{2+}, Fe^{2+}, $Cr_2O_7^{2-}$, (10 folds). The results show that most of the cations and anions used have no considerable effect on the determination of minoxidil, while Cu^{2+}, V^{4+} and MoO_4^{2-} do interfere.

Application: The proposed method was applied to the determination of minoxidil content of 10 mg minoxidil tablets, (from Chemi Daruo Co). The results are shown in Table-2. As it is seen, there is a satisfactory agreement between the results of the proposed method and the reference value of minoxidil content of the formulations.

TABLE-2
DETERMINATION OF THE MINOXIDIL CONTENT OF 10 mg FORMULATION TABLETS BY THE PROPOSED METHODS

Sample	Reference amount (mg)	Obtained (mg)	Recovery (%)
1	10	10.30	103.0
2	10	10.35	103.5
3	10	10.40	104.0

Conclusion

The method described, provides a simple and reliable means of determination of trace amounts of minoxidil in formulation samples. The limit of detection of the proposed method seems to be very good. The method compares favourably in sensitivity and selectivity with most of the published methods[4-9] for the determination of minoxidil and it can certainly be placed among the most sensitive ones.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the financial support of this work by Payame Noor University Research Council.

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(*Received*: 24 July 2007; *Accepted*: 4 February 2008) AJC-6291