Spectrophotometric method for the determination of tolnaftate in pharmaceutical preparations

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Received 19 / 05 / 2013
Accepted 04 / 09 / 2013

الخلاصة

تم تطوير طريقة طيفية بسيطة وسريعة وذات حساسية و دقة عالية لتقدير التولنافتيت في صورته النقية وفي مستحضراته الصيدلانية. تعتمد الطريقة على أكسدة التولنافتيت بواسطة برمنكنات البوتاسيوم في الوسط القاعدي لتعطي ناتج لونه اخضر مزرق والذي له أقصى امتصاص عند 610 نانوميتر. ووجد بأن قانون بير ينطبق ضمن مدى التراكيز من 5 الى 60 مايكرو غرام/مل وبلغت قيمة الامتصاصية المولارية 5.379×10^4 لتر.مول$^{-1}$.سم$^{-1}$ وتم دراسة الظروف المثلى للتفاعل وطبقت الطريقة بنجاح لتقدير التولنافتيت في بعض مستحضراته الصيدلانية. وتم إجراء مقارنة إحصائية بين نَتائِجِ هذه الطريقة ونتائج الطريقةِ القياسية الدستورية المعتمدة لاختبار نجاح الطريقة باستخدام اختباري (t) و(F) عند حدود ثقة 95% وكانت القيم اقل مما هي في الجداول الاحصائيه مما يدل على صلاحية التطبيق التحليلي للطريقة في التحليل الروتيني في السيطرة النوعية لتقدير التولنافتيت بحالته النقية وفي بعض مستحضراته الصيدلانية كما وجد عدم وجود تداخل للمضافات الدوائية في ألطريقه المقترحة.

Abstract

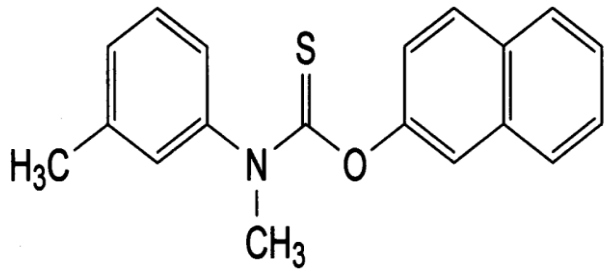
A simple, accurate, rapid and sensitive visible spectrophotometric method has been developed for the determination of tolnaftate in pure and pharmaceutical preparations. The method is based on the reaction of tolnaftate with potassium permanganate in alkaline medium to form a bluish green colored product with an absorption maximum at 610 nm. Beer's law was obeyed in the range of 5-60 µg/25ml with a molar absorbitivity of 5.379×10^4 L.mol.$^{-1}$.cm^{-1}. The optimum conditions for all color development were described and the proposed method has been

successfully applied for the determination of tolnaftate in pharmaceutical preparations. A statistical comparison of these results with those of official method using (t and F) values at 95% confidence level, The calculated t- and F- values did not exceed the theoretical values indicating that there was no significant differences between the precision of the proposed and official method. So that the proposed method can be used as a routine quality control for determination of tolnaftate in pure form and in pharmaceutical formulations.The common excipients and additives did not interfere in the proposed method.

Keywords: Tolnaftate, **Potassium permangnate, Spectrophotometric**

Introduction

Tolnaftate is *O*-2-naphthyl methyl(3-methylphenyl) thiocarbamate, and has the following chemical structure:-



$C_{19}H_{17}NOS$= 307.4 g/mol.

Tolnaftate is an antifungal and used topically in the treatment of cutaneous disease such as jock itch, athlete's foot [1,2], the other skin infections due to, e*pidermophyton*, *Microsporum*, *Trichophyton* species, and *Malasseziafurfur*. [3,4]. The analytical methods used for tolnaftate assay in pharmaceutical formulations mainly employ high performance liquid chromatography (HPLC) [5-9] and (HPTLC) [10]. USP 33 and Bp (2013) prescribes UV spectrophotomeric determination of tolnaftate in cream and gel at 258 nm after appropriate extraction.[11,12], a survey of literature revealed that only a few visible spectrophotometric methods were reported [13-15] and spectrofluorimetry method has been also used [16]. The present method described a simple, economical, accurate, sensitive and reproducible spectrophotometric method for the determination of tolnaftate in pharmaceutical preparations. The method based on the oxidation of tolnaftate by a potassium permanganate in alkaline solution to form a bluish green colored product with an maximum absorption at 610 nm.

EXPERIMENTAL

Apparatus

Optima sp-3000 plus UV-visible spectrophotometer with 1.0 cm quartz cells were used for all absorption measurements.

Reagents

All chemicals used were of analytical reagent grade. A standard solution of tolnaftate (100 ppm) was prepared by dissolving 0.0100 g of pure drug in 100 mL ethanol. It was later diluted with water to get concentration of 10 ppm. Potassium permanganate about 0.01M. This solution was prepared by dissolving 1.6 g in 1L distilled water, Then the solution was heated to boiling and then filtered through asbestos. The filtered solution should be kept in the dark and standardized immediately before use. [17]. Sodium hydroxide (2 N). This solution was prepared by dissolving 8 g of pure NaOH in 100 ml distilled water.

Recommended procedures

Different aliquots of standard tolnaftate solution equivalent to 5-60µg were transferred into a series of 25ml volumetric flask, 5 ml of 2N NaOH and 3 ml of 0.01M $KMnO_4$ were added. The content was mixed and let stand for 5 min with occasional shaking. The volume was diluted to the mark with distilled water and mixed well. The absorbance of each solution was measured at 610 nm against a reagent blank.

Procedures for pharmaceutical preparations:

Creams:

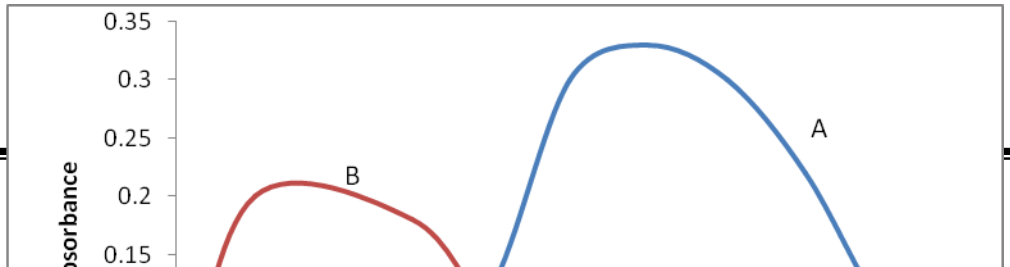
1gm of cream, equivalent to 10 mg of tolnaftate was transferred to 250 ml separating funnel containing 75 ml chloroform. The chloroform solution successively washed with two portions (25ml) of 0.1 N NaOH, two 25 ml portions of 0.1N HCl and 25ml of water. The chloroform layer was filtered through a chloroform-washed cotton pledged into a 100 ml volumetric flask. Chloroform was added to volume, and mixed,10 ml of chloroform solution was evaporated on a steam bath just to dryness and the residue was dissolved in 20 ml of ethanol and diluted to 100 ml with ethanol [11], 3ml of this solution was treated as mentioned under recommended procedure.

Topical solutions:

A 1.0 ml of solution containing 10 mg of tolnaftate was transferred into100 mL volumetric flask and diluted up to mark with ethanol,3ml of this solution was treated as mentioned under recommended procedure.

Results and Discussions

The reaction between tolnaftate and $KMnO_4$ in alkaline medium yields a green color dye due to the formation of manganate ions, which have maximum absorption at 610 nm Fig.(1).



Fig(1):Absorption spectra of (A) -Tolnaftate (40µg/25ml) with$KMnO_4$ against blank. (B) - Blank against distilled water.

The various experimental parameters affecting the development and stability of the reaction product was optimized by changing each variable in turn while keeping all other variables constant.

Effect of $KMnO_4$ concentration

The absorbance increase with increasing $KMnO_4$ concentration. It was found that 3 ml of 0.01M $KMnO_4$ was adequate for the maximum absorbance for the dye formed.

Effect of NaOH

Trials were made to determine the drug through oxidation with $KMnO_4$ in neutral, acidic and alkaline media, oxidation of tolnaftate was observed in alkaline medium (NaOH) compaired with neutral and acidic mediums. It was found that increasing the volume of 2M NaOH would increase absorbance of the reaction product up to 5 ml. after that NaOH has no effect on the absorbance, therefore 5 ml was selected for the subsequent experiments.

Effect of temperature

The resulting product of the proposed method was studied at room temperature (25±5 C^0), Higher temperature causes turbid color, therefore, room temperature was selected as a suitable temperature.

Effect of reaction time

The color formed immediately after addition of potassium permanganate and became stable after 5 minutes, therefore 5 minutes as a development time was selected as a suitable time in the recommended procedure, the color obtained was stable for at least 3 hours.

Order of addition

To test the order of addition on the absorbance of the product, different orders were tested. The selected order was sample solution, NaOH followed by $KMnO_4$ solution which was gave high absorbance value.

Calibration graph

Employing the conditions described in the recommended procedure a linear calibration graph of tolnaftate is obtained Fig.(2), which shows that Beer's law is obeyed over the concentration range 5-60 µg/25ml with determination coefficient of 0.999, intercept of 0.016 and slope of 0.007.

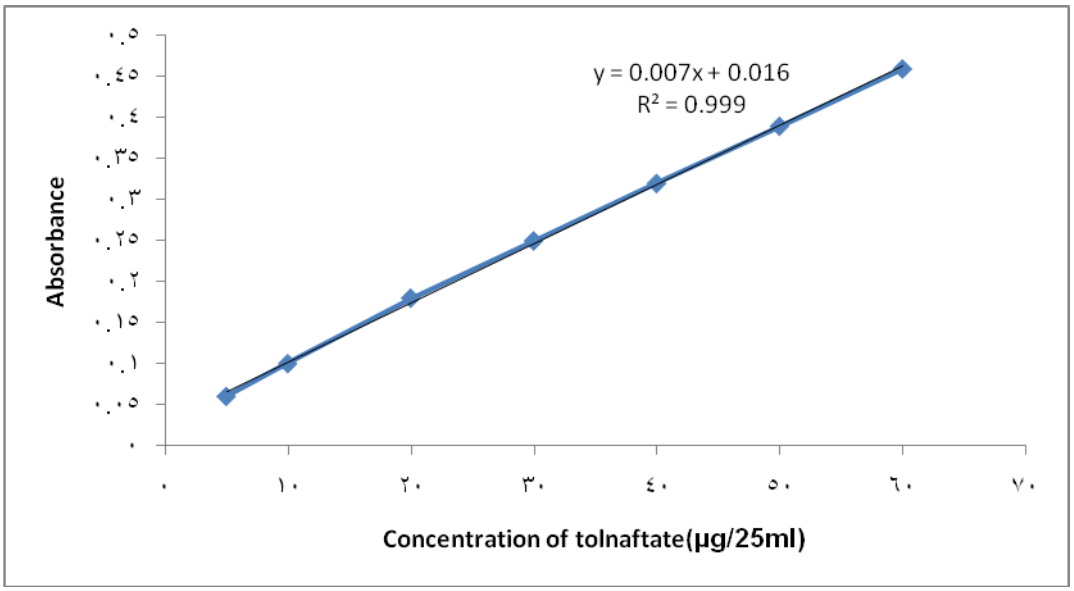


Fig. (2): Calibration curve for tolnaftate

The limits of detection (LOD) and quantification (LOQ) were calculated using the following formulae: LOD= (3.3σ/s) and LOQ=(10 σ/s) where σ is the standard deviation of the blank and s is the slope of the regression line [18]. Limit of detection (LOD) and limit of quantification (LOQ) were found 0.02 µg/ml and 0.06 µg/ml respectively. The conditional molar absorptivity of the product formed was found to be 5.379×10^4 L. $mol^{-1}.cm^{-1}$.

Accuracy and Precision

To evaluate the accuracy and precision of the method, a pure drug solution was analyzed at three different concentrations, each determination being repeated six times the relative error (%) and relative standard deviation (%) values were summarized in Table (1). From Table (1), it is clear that the relative error of less than 1.9% and the method was found to be precise with RSD value not more than 1.8%. for a better picture of reproducibility, a series of experiments were performed in

which the standard drug solution was determined at three different levels each day for six days, with all solutions being prepared a fresh each day. The day-to-day relative standard deviation values were in the range of 0.8-1.8 % and represent the best appraisal of repeatability of the proposed method.

Table(1): Accuracy and precision of the method

Tolnaftate taken, µg/25ml	E_r (%)[a]	RSD [a] %
10	1.2	1.3
30	1.5	1.7
50	1.8	1.5

a: Mean of six determinations

Effect of interferences

The interfering effect of foreign species often accompanied with tolnaftate in the pharmaceutical preparations were studied by adding different amounts of foreign species to 30µg\ 25ml of tolnaftate in solution and the recommended procedure for the determination of tolnaftate was followed. The species are considered to interfere seriously if they cause a change of more than 2% in the absorbance obtained for tolnaftate a lone [19]. It was observed that the betamethazone 17-valerate, gentamycine sulphate and clioquinol don't interfere with determination method at levels found in the dosage form cited in Table(2) so that the selectivity of method is very good.

Table [2]: Determination of tolnaftate in presence of excipients.

Excipients	Amount taken, µg	Average recovery*, %
Betamethazon 17-valerate	30	100.05
Gentamycine sulphate	60	100.0
Clioquinol	50	100.08

* Average of seven replicate analyses.

Analytical applications

The proposed method was satisfactorily applied to the determination of tolnaftate in its pharmaceutical formulations. The results of the assay of the pharmaceutical formulations revels that there was closed agreement between the results obtained by the proposed method and the label claim. The results were also compared statistically by student t-test and by the variance ratio F-test with those obtained by official method [11] at 95% confidence level. The calculated t- and F-values did not exceed the theoretical values indicating that there was no significant differences between the precision of the proposed and official method as cited in Table(3).

Table(3): Determination of tolnaftate in pharmaceutical formulations

Pharmaceutical formulations(NDI)	Label amount, mg	Official method [11]	Proposed method *	F-value	t-value
Quadreem cream	10mg/gm	9.98	9.96	1.02	1.14
Topical solution	10mg/ml	9.94	9.95	1.06	1.95

*Mean value of ten determinations

t values (n=10, at 95% confidence level tabulated value 2.101).

F values (n_1-1 and n_2-1 =9, at 95% confidence tabulated value 3.18).

Conclusion

The proposed method was simple, accurate, precise, sensitive and low economical cost. Furthermore, the proposed method doesn't require elaboration of procedures, which are usually associated with chromatographic methods. The proposed method could be applied successfully for determination of tolnaftate in pure form as well as in different dosage forms.

Acknowledgments

The first author wishes to express gratitude to his former company [The State Company of Drug Industries and Medical Appliance (NDI) Nineveh – Iraq for providing gift samples of tolnaftate standard material and pharmaceutical preparations

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