Simple Spectrophotometric Methods for Determination of Tolterodine Tartrate in Pharmaceutical Forms

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Abstract: Simple, fast and reproducible methods were developed for the determination of Tolterodine tartrate (TOL), the first method (method A) was based on the oxidation of the drug using permanganate in acidic medium in the presence of methylene blue dye and estimation of (TOL) by measuring the absorbance of the residual amount of methylene blue dye at 600 nm, in (method B) the drug amount was estimated by measuring the residual amount of permanganate which absorbs at 540 nm in basic medium. The calibration of the methods using beer's law was investigated in the ranges of 12-60 and 5-50 µg/ml and Limits of detection of 3.6 and 2.2 µg/ml for method A and method B respectively.
Key words: Tolterodine tartrate, Permanganate, Oxidation, Pharmaceutical.

Introduction

Tolterodine tartrate (TOL) is chemically (R)-2-[3-[bis(1-methylethyl)-amino]1-phenylpropyl]-4-methylphenol [R-(R*,R*)]- 2,3dihydroxybutanedioate (1:1) (fig.1), is a selective muscarinic receptor antagonist and thus prevents the frequent urinations, it was the first drug used for the treatment of overactive bladder (OAB)[1,2] and it was listed in Merck index and considered to exist in two isomeric forms R and S[3], Tolterodine tartrate has been determined using various methods which include advanced techniques such as capillary chromatography[4,5], gas chromatography[5,6], liquid chromatography–mass spectrometry[7-12], and few spectro photometric was developed based on UV[13], charge transfer complexation[14] and other spectrophotometric methods[15-18].
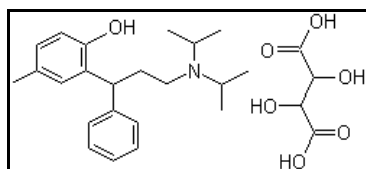

Fig. 1 Chemical Structure of (TOL)

Most analytical methods in the literature are based on sophisticated and expensive techniques and require extraction steps. The aim of the present work was to develop a simple, fast and validated alternative method for the estimation of (TOL) in pharmaceutical dosage form without the need of complicated procedures. The new methods are aimed to be applied for routine quality control tests in simple dosage forms where the composition of samples is well known and doesn't require such a low detection limit for determination.

Experimental

Reagents:

All chemicals used were analytical grade and were purchased from scharlau, distilled water was used as solvent to prepare all solutions. Pharmaceutical grade was purchased from a local pharmacy (Detrol®)

Preparation of reagents:

200 ppm stock solution of Tolterodine tartrate was prepared daily, 0.04 M NaOH solution was used. Freshly prepared solution of potassium permanganate was prepared by dissolving 0.066 g in 250 ml water, Methylene blue dye was prepared by dissolving 0.02 g in 100 ml of water (200 ppm)

Apparatus:

A UV-VIS double beam spectrophotometer (Labomed 3500) with 1 cm quartz cells with spectral bandwidth of 2 nm and wavelength correction of ±0.2 nm, wavelength range (190-1100nm)

Calibration curves:

Method A:

Into a series of 10 ml volumetric flasks 1.0 ml of $KMnO_4$, and 2 ml Sulfuric acid solutions were pipetted, then different volumes of (TOL) standard solution were added, the mixture was stand for 20 minutes then 2 ml of Methylene blue dye was added and finally water was added to complete the volume to 10.0 ml. the mixture was shacked then the absorbance was measured at 600 nm.

Method B:

Into a series of 10 ml volumetric flasks 2.0 ml of $KMnO_4$, and 2 ml of NaOH solutions were pipetted, then different volumes of (TOL) standard solution were added finally water was added to complete the volume to 10.0 ml. Then the mixture was shocked, then the absorbance was measured at 610 NM after 20 minutes.

Methods for dosage forms:

An amount equivalent to 2.0 mg of (TOL) of finely ground tablet or capsules was accurately weighed and transferred into 100 ml volumetric flask, the mixture was stirred for 30 minutes , then kept for five minutes and filtered using 0.5 µm filter paper, finally a certain portion of the filtrate was taken and used as the procedure proposed for the procedure proposed for construction of the calibration curve above.
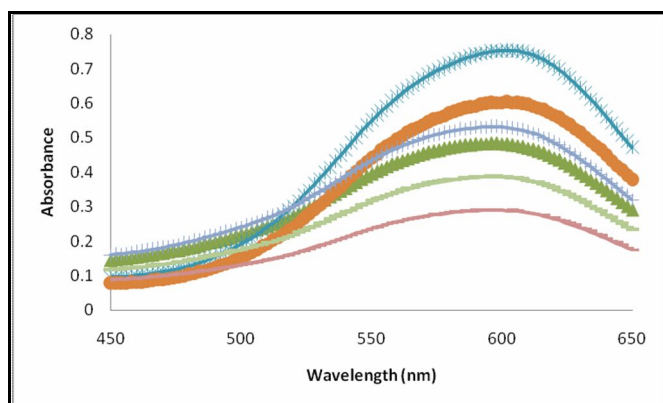
Results and Discussion

Fig. 2: Effect of (TOL) on Absorption at 600nm (Method A)

Tolterodine tartrate doesn't have absorption in the visible region, in this work spectrophotometric methods based on using permanganate as an oxidant, since (TOL) can be easily oxidized due to the presence of phenol group as shown in (Figure 1). Permanganate ion (MnO_4^-) has two strong absorption peaks at 525 and 540 nm as shown in figure 2 below. It can be reduced in both acidic and basic media. In acidic medium it is

reduced to Mn^{2+} which has pale yellow color and unstable in solution, in basic medium (MnO_4^-) reduced to manganate ion (MnO_4^{-2}) which has violet to green color having absorption at 610 nm. Base on that two spectrophotometric methods were developed for the estimation of (TOL) utilizing its reaction with permanganate. In the first method (Method A) the reaction of (TOL) with excess amount of permanganate in sulfuric acid solution, after that methylene blue dye which is bleached by permanganate was added in excess amount, and thus the residual amount of the dye is proportional to the initial concentration of (TOL), the mount of the dye was determined by measuring its absorbance at 600 nm which is far away from interferences the results are shown in (fig. 2.) In method B (TOL) solution was treated with alkaline permanganate was used to oxidize (TOL), as a result manganate ion start forming and appears as violet-green color having maximum absorbance at 610 nm as shown in (fig. 3). The oxidation of (TOL) using alkaline permanganate proceeds slowly at room temperature and completed above 16 minutes as shown in (fig. 4).
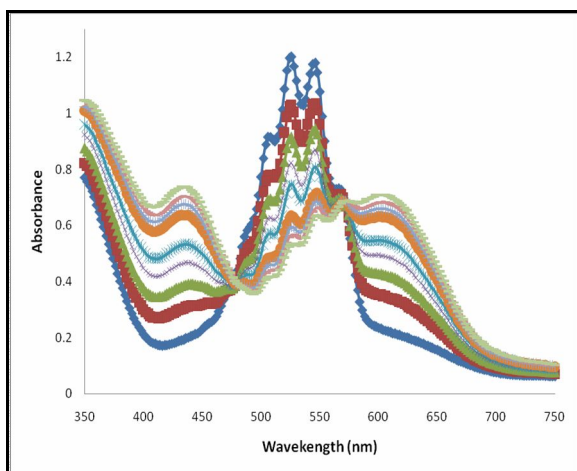

Fig. 3: Effect of (TOL) on Absorption spectrum (Method B)

Optimization of the experimental conditions

All the experimental variables affecting the absorbance were studied using univariant analysis. For (method A) the concentration effects of permanganate, sulfuric acid and (MB) were studied separately using fixed amount of (TOL), each variable was studied while keeping the amounts of the other reagents constant in order to obtain the optimum amounts of all reagent that give maximum range of absorbance at 600 nm with minimum amount of permanganate to minimize interfering, the optimum reagents volumes were 1 ml of 0.017 M $KMnO_4$, 2.0 ml of 0.5 M H_2SO_4 and 2 ml of 200 mg/l of (MB) the effect of volume of (MB) was studied as shown in (fig. 4) In (method B) both the concentration of NaOH and permanganate solutions were investigated separately in a series of constant (TOL) concentrations, the optimum amounts were 2 ml of 0.028 M of NaOH and 2.0 ml of 0.017 M of permanganate, (fig. 5) shows the effect of changing the volume of permanganate keeping all other factors constant. The effect of time was investigated by monitoring the absorbance of permanganate at 540 nm during the reaction with (TOL) as shown in (fig. 6) In (method B) the calibration curve can be obtained by either monitoring the increase of the absorbance of manganate ion at 610 nm or monitoring the decrease of the absorbance of permanganate at 540 nm, the latter method was selected due to higher sensitivity.
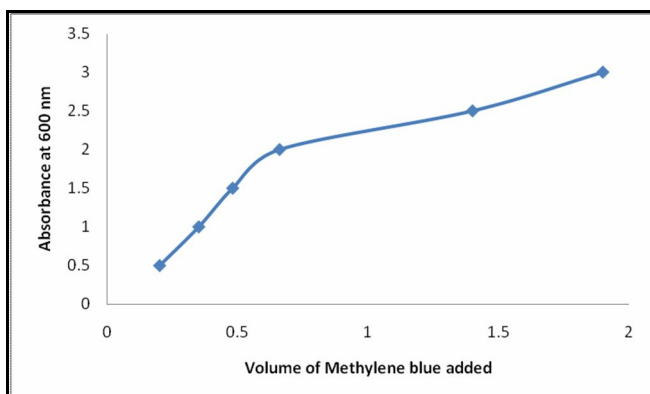

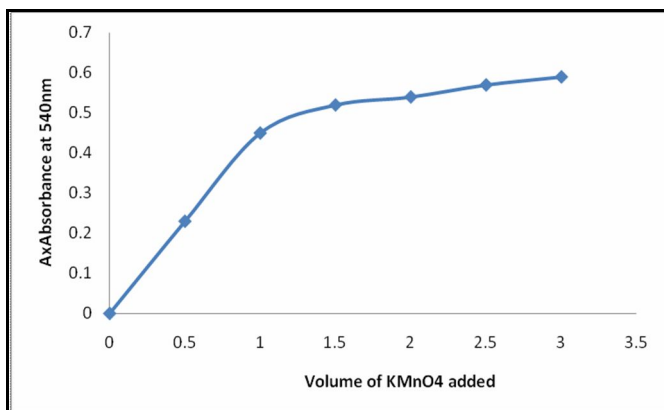**Fig. 4: Effect of volume of (MB) dye on absorption at 600nm (Method A)**

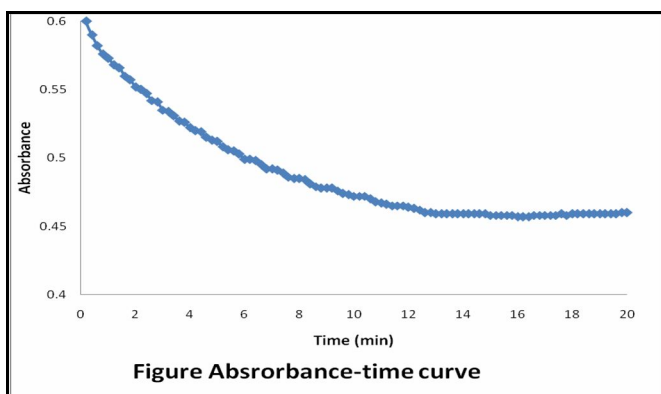**Fig. 5: Effect of volume of (KMnO₄) on absorption at 540 nm (Method B)**

Fig. 6: Effect of Time on absorption of KMnO₄ at 540 nm (Method B)

Quantification:

Using the optimized reagent concentrations, the calibration curves were constructed for the determination of (TOL) for both Methods A and B.   Regression data are shown in (Table 1)

Table 1: Regression data for the suggested methods

Parameter	Method A	Method B
Wavelength (nm)	600	540
Slope	0.0084	-0.176
Intercept	0.316	0.632
R^2	0.99	0.98
Dynamic Range (µg/ml)	12-60	5-50
LOD	3.6	2.2
LOQ	12.1	7.3

The proposed methods were validated by comparing the results of real pharmaceutical samples using the reference HPLC method [12]. The data are shown in (Table 2).

Table 2: Comparison between suggested methods and standard method using 5 replicates

Drug	Method A	Method B	Standard method
Amount taken (mg)	50	50	50
Recovery %	98	97	98
t-value*	1.57	2.14	

* t-value for five replicates is 2.57

Conclusion

Tolterodine tartrate was determined in pure and dosage forms utilizing the its oxidation reaction with permanganate in acidic and basic media. The proposed methods were simple, low cost, sensitive and was validated and compared with reference methods.

Acknowledgment

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