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NEW SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF TOLTERODINE IN BULK AND PHARMACEUTICAL FORMULATION

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ABSTRACT

Simple, fast and economic spectrophotometric methods were developed for determination of Tolterodine in bulk and pharmaceutical dosage forms using water as the solvent. The quantitative determination of the drug was carried out using the zero order derivative measured at 281.5 nm, first order derivative measured at 274 nm and area under curve was measured in wavelength range of 276-286 nm. Calibration graphs constructed were linear in the concentration range 30-180 µg.mL^{-1} with r^2 = 0.9998, r^2 = 0.9998 and r = 0.9997 for zero order, first order derivative and area under curve method respectively. All the proposed methods have been extensively validated as per ICH guidelines. There was no significant difference between the performance of the proposed methods regarding the mean values and standard deviations.

INTRODUCTION: Tolterodine is an antimuscarinic drug that is used to treat urinary incontinence. Tolterodine acts on M1, M2, M3, M4 and M5 subtypes of muscarinic receptors whereas modern antimuscarinic treatments for overactive bladder only act on M3 receptors making them more selective. Tolterodine is chemically 2-[(1, S)-3-(di-isopropylamino)-1-phenyl propyl]-4-methylphenol (**Fig. 1**). The molecular formula of Tolterodine is $C_{22}H_{31}NO$. The molecular mass of Tolterodine is 325.488 g/mol [1]. It is soluble in water, methanol, slightly soluble in ethanol [2]. Literature survey reveals that, only spectrophotometric methods [3, 4], some analytical methods [5-7] and few bio analytical methods [8] have been reported for quantitative estimation of Tolterodine in bulk drug and pharmaceutical formulation. Hence an attempt has been made to develop new spectrophotometric methods for its estimation in bulk and pharmaceutical formulation with good precision, accuracy, linearity and reproducibility.

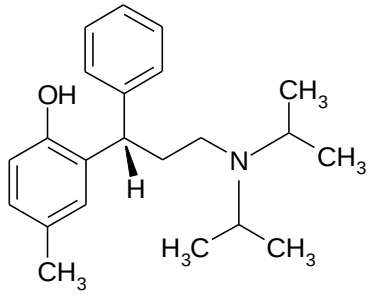

FIG 1: CHEMICAL STRUCTURE OF TOLTERODINE

MATERIALS AND METHODS: Tolterodine pure compound was kindly supplied by Health Care Formulation Limited, Vadodara, Gujarat, India and was used without further purification. Distilled water was used as solvent.

INSTRUMENTATION: For all the spectrophotometric methods, Shimadzu model 1700 double beam UV-VIS spectrophotometer with spectral bandwidth of 1.8nm, wavelength accuracy of 2 nm and a pair of 1 cm matched quartz cells of 10 mm optical path length was used.

Preparation of standard and sample solutions: Stock solution of 1000 µg.mL^{-1} of Tolterodine was prepared in water for zero order, first order derivative and area under curve method for spectrophotometric analysis of Tolterodine.

The standard solutions were prepared by dilution of the stock solution with water in a concentration range of 30, 60, 90, 120, 150 and 180 µg.mL^{-1} with water for zero order, first order derivative and area under curve method. Distilled water was used as a blank solution.

Assay procedure: 25 tablets were powdered and an amount equivalent to 50 mg of Tolterodine was accurately weighed and dissolved in approximately 25 ml of water in 50 ml volumetric flask and sonicated for 5 minutes, then it was diluted up to the mark with distilled water to obtain 1000 µg/ml solution**.**

The solution was filtered through Whatmann filter paper No.41. An appropriate dilution was made to obtain 90 µg.mL^{-1} with water from stock solution for zero order, first order derivative and area under curve method.

RESULTS AND DISCUSSION: The zero order spectra and first order spectra for Tolterodine were recorded at the wavelength of 281.5 nm and 274 nm respectively (**Fig. 2, 3**). The area of Tolterodine was selected in wavelength range of 276-286 nm (**Fig.4**).

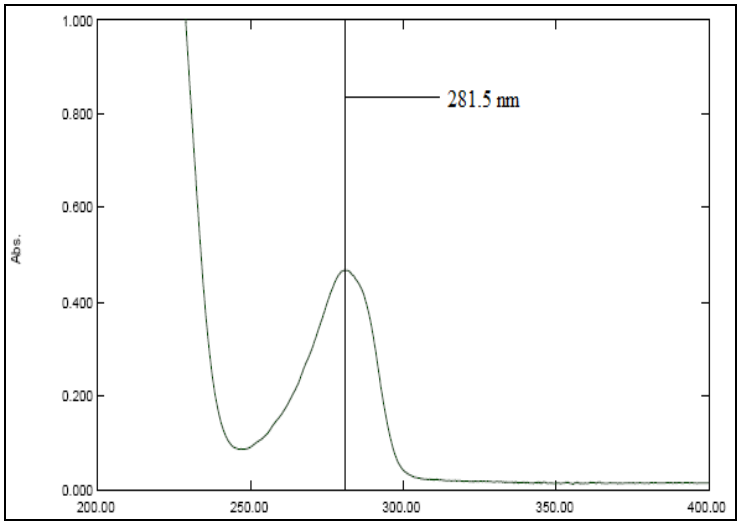

FIG. 2: ZERO ORDER SPECTRUM OF 90 µg/ml OF TOLTERODINE IN WATER

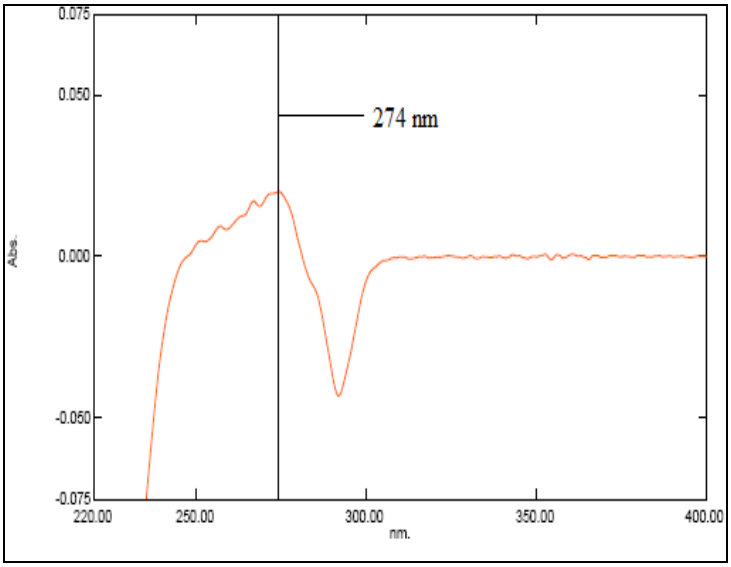

FIG. 3: FIRST ORDER DERIVATIVE SPECTRUM OF 90 µg/ml OF TOLTERODINE IN WATER

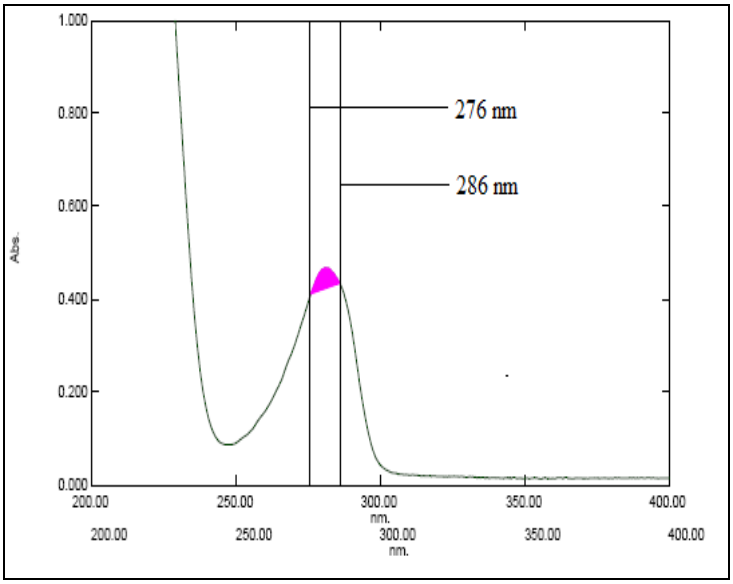

FIG. 4: AREA UNDER CURVE SPECTRUM OF 90 µg/ml OF TOLTERODINE IN WATER

Linearity and Range: Under the experimental conditions described, the graph obtained for zero order, first order derivative and area under curve showed linear relationship (**Fig. 5, 6, 7**). Regression analysis was made for the slope, intercept and correlation coefficient values. The regression equations of calibration curves were y = 0.005x + 0.002 (r^2 = 0.9998) at 281.5 nm for zero method and y = 0.002x + 0.001(r^2 = 0.9998) for first order derivative method and y = 0.003x + 0.006 (r^2 = 0.9997) for area under curve method. The range was found to be 30-180 µg.mL-1 for zero order, first order derivative and area under curve method (**Table 1**).

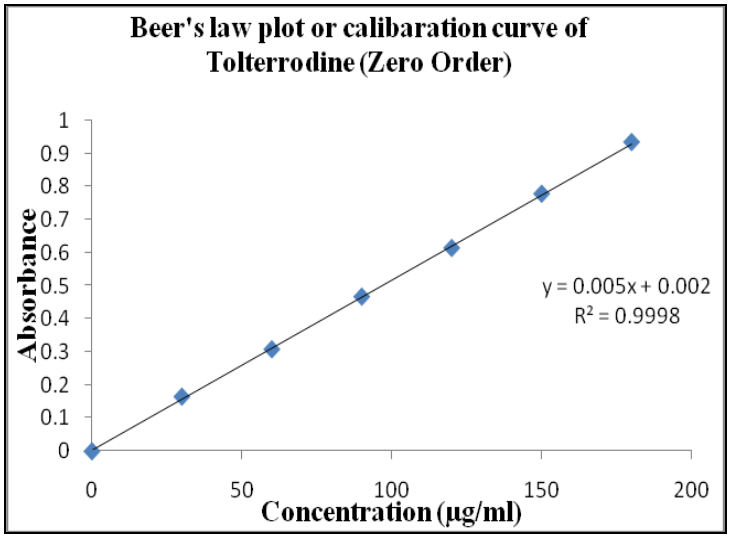

FIG. 5: CALIBRATION CURVE OF TOLTERODINE FOR ZERO ORDER METHOD

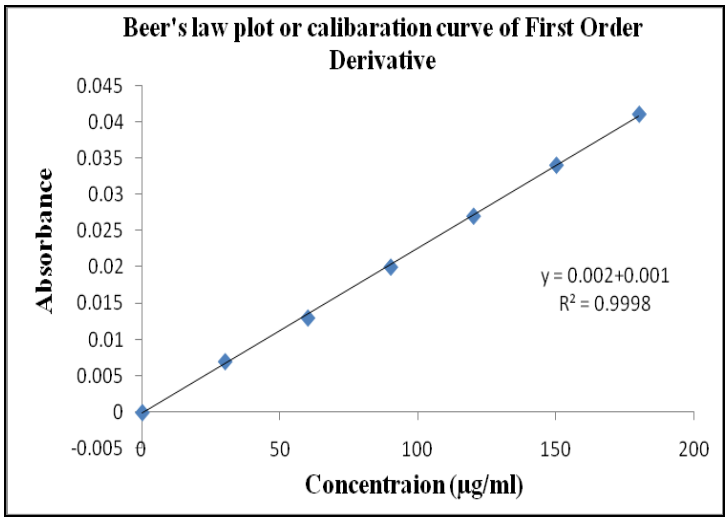

FIG. 6: CALIBRATION CURVE OF TOLTERODINE FOR FIRST ORDER DERIVATIVE METHOD

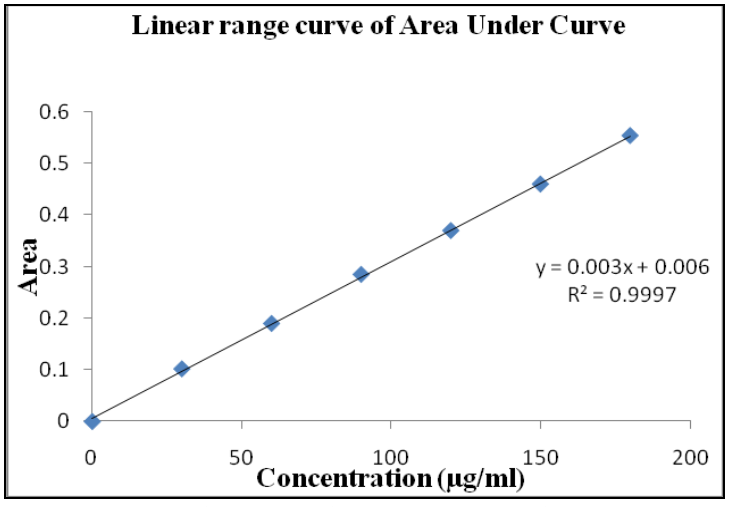

FIG. 7: CALIBRATION CURVE OF TOLTERODINE FOR AREA UNDER CURVE METHOD

TABLE 1: STATISTICAL DATA FOR THE CALIBRATION GRAPHS FOR DETERMINATION OF TOLTERODINE BY PROPOSED METHODS

Parameters	Zero Order	First Order	Area Under Curve
Linearity range (µg/ml)	30-180	30-180	30-180
Correlation co-efficient (r^2)	0.9998	0.9998	0.9997

n=3

Precision: To determine the precision of the method, Tolterodine solutions at a concentration of 90 µg.mL^{-1} were analyzed each six times for zero order, first order and area under curve method. Solutions for the standard curves were prepared fresh everyday (**Table 2**).

TABLE 2: RESULTS OF INTRA AND INTER DAY PRECISION

Parameters	Intra Day Precision		Inter Day Precision	
	S.D.	% RSD	S.D.	% RSD
Zero derivative	0.0568	0.0571	0.0635	0.0692
First derivative	0.6122	0.6570	0.9465	0.9538
Area Under Curve	0.6226	0.6399	0.7541	0.7525

n=3

Sensitivity: The limit of detection (LOD) and limit of quantification (LOQ) were calculated by using the equations LOD = 3 x σ / S and LOQ = 10 x σ /S, where σ is the standard deviation of intercept, S is the slope. The LOD and LOQ were found to be 0.660 µg.mL^{-1} and 2.000 µg.mL^{-1} respectively for zero order derivative and the LOD and LOQ were found to be 1.143 µg.mL^{-1} and 3.464 µg.mL^{-1} for first order derivative methods respectively and LOD and LOQ were found to be 0.6350 µg.mL^{-1} and 0.6350 µg.mL^{-1} respectively for area under curve method.

Recovery: To study the accuracy of the proposed methods, and to check the interference from excipients used in the dosage forms, recovery experiments were carried out by the standard addition method. This study was performed by addition of known amounts of Tolterodine to reanalyzed solutions of commercial by available tablets (**Table 3**).

Analysis of the marketed formulation: There was no interference from the excipients commonly present in the tablets. The drug content was found to be 99.91% with a % R.S.D. of 0.19 and 99.97% with a % R.S.D. of 0.11 for zero order and first order derivative spectrophotometric methods respectively. It may therefore be inferred that degradation of Tolterodine

had not occurred in the marketed formulations that were analyzed by this method. The low % R.S.D. value indicated the suitability of this method for routine analysis of Tolterodine in pharmaceutical dosage form (**Table 4**). The summary of the validation parameters is depicted in (**Table 5**).

TABLE 3: DATA OF RECOVERY STUDY FOR TOLTERODINE

Actual Concentration (µg/ml)	Observed Concentration (µg/ml)	% Recovery	RSD*
Zero Order			
3.6	3.592	99.50	0.7477
4.0	4.010	100.25	0.9802
4.4	4.358	99.05	0.4884
First Order			
3.6	3.596	99.88	0.3638
4.0	3.967	99.18	0.2765
4.4	4.380	99.20	0.4501
Area Under Curve			
3.6	3.662	100.06	0.1989
4.0	3.994	99.73	0.2765
4.4	4.377	99.48	0.1462

n=3

TABLE 4: ASSAY RESULTS OF INTRA AND INTER DAY PRECISION

Formulation	Method	Label claim (mg)	Amount found (mg)	% Amount found
	Zero derivative	2	1.991	99.55
	First derivative	2	1.980	99.00
	Area Under Curve	2	1.988	99.40

TABLE 5: CALIBRATION PARAMETERS

Parameters	Zero Order	First Order	Area Under Curve
Wavelength (nm)	281.5	274	276-286
Linearity (µg.mL^{-1})	30-180	30-180	30-180
Correlation Coefficient	0.9998	0.9998	0.9997
LOD (µg.mL^{-1})	0.6600	1.1431	0.6350
LOQ (µg.mL^{-1})	2.0000	3.4641	1.9245
Mean Recovery	99.5666	99.5677	99.6399

CONCLUSION: Simple, fast, reliable and accurate spectrophotometric methods were developed for the routine determination of Tolterodine. The developed methods can be concluded as accurate, sensitive and precise and can be easily applied to the pharmaceutical formulation.

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