Vol 4, Issue 5, 2017 ISSN 2349-7041

Research Article

SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF TRAZODONE HYDROCHLORIDE IN PRESENCE OF ITS ALKALINE DEGRADATION PRODUCT

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ABSTRACT

Introduction: Simple, sensitive, precise and low-cost spectrophotometric methods were developed for the determination of trazodone hydrochloride in the presence of its alkaline degradation product in bulk powder and in a pharmaceutical preparation. The proposed spectrophotometric methods involve, second derivative (2D), ratio derivative (1DD), ratio difference, Mean centering, bivariate and dual wavelength. **Results and discussion**: The regression plot was found to be linear over the range of 1-30 μg mL^{-1} Conclusions. These methods were validated and successfully applied for the determination of trazodone hydrochloride Trittico ® tablets. The obtained results were statistically compared with those of the reported method by applying t-test and F-value at 95% confidence level, and no significant difference was observed regarding accuracy and precision.

Keywords: Trazodone hydrochloride, Second derivative, Ratio derivative, Ratio difference, Mean centering, Bivariate, Dual wavelength.

INTRODUCTION

Trazodone, (2-{3-[4-(3-chlorophenyl) piperazin-1-yl] propyl}-2H, 3H-[1, 2, 4] triazolo [4, 3-a] pyridin-3-one), is a well-known chemical compound that is used as an antidepressant that belongs to a selective serotonin reuptake inhibitors (SARI) [1]. Trazodone is used as anti-anxiety and sleep-inducing (hypnotic) agent [1]. The official method for analysis of trazodone hydrochloride based on potentiometric non-aqueous titration with perchloric acid [2] and HPLC using octadecylsilane column and water-0.01 M ammonium phosphate buffer pH 6.0 (60: 40) as mobile phase [3]. Analytical methods that are reported for the determination of trazodone hydrochloride in pharmaceutical formulations include spectrophotometric methods [4-7] ion-selective electrode [8, 9] voltammetry [10-13] and various chromatographic methods including; HPLC [3, 14-17] capillary gas chromatography [18], mass spectrometry [19] and instrumental thin layer chromatography [20]. Also, spectrofluorimetric methods have been reported [21, 22].

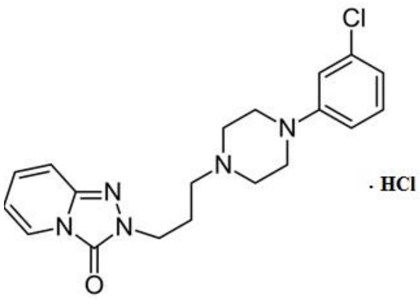


Fig. 1: Structural formula of trazodone hydrochloride.

MATERIALS AND METHODS

Apparatus

- Shimadzu UV-Vis. 1650 Spectrophotometer (Japan).
- Hot plate (Torrey pines Scientific, USA).
- Jenway, pH meter 3510 (USA).
- Rotary evaporator (scilogex , USA)

MATERIALS AND CHEMICALS

- Trazodone hydrochloride powder was kindly supplied by Egyptian International Pharmaceutical Industries Company (Eipico) 10th of Ramadan City, Egypt. Its purity was 100.35±0.20 %.(Batch. NO.A0967912).
- Trittico ® tablets, labeled to contain 50 mg of trazodone hydrochloride per tablet manufactured by Egyptian International Pharmaceutical Industries Company (Eipico) 10th of Ramadan City, Batch No.1602038 and purchased from the local market.
- Hydrochloric acid and sodium hydroxide (El-Nasr Co., Egypt) prepared as a 2*M* aqueous solution.

Standard Solution

A stock standard solution of trazodone hydrochloride (1 mg mL^{-1}) was prepared by dissolving 100 mg of trazodone hydrochloride in 50 ml of water, and the volume was completed to 100 mL with water. Working solution (0.1 mg mL^{-1}) was prepared by transferring 10 mL of the standard stock solution into 100 mL volumetric flask, and then the volume was completed to the mark with water.

Degraded Sample [17]

Alkaline-induced forced degradation was performed by adding 100 mg of trazodone hydrochloride to 50 mL of 2 M NaOH and refluxing at 80°C for approximately 17 hours. The solution was then left to reach ambient temperature, neutralized to pH 7 by an addition of 2 M HCl, evaporated to dryness, the residue was extracted three times with 25 mL of water, then filtered into 100 -mL volumetric flask then the volume was adjusted by the same solvent. The obtained solution was labeled to contain 1 mg mL^{-1} of trazodone hydrochloride degradation product derived from.

PROCEDURES

Construction of the Calibration Curves (General Procedures)

Second derivative method: Aliquots of standard trazodone hydrochloride solution (100 μg mL^{-1}) containing (10 – 300) μg of the drug were added to a series of 10- ml volumetric flasks and then diluted to the mark with water. The second - derivative of the absorption spectra (from 200 to 400 nm) was measured using water as a blank. The amplitude of the trough at 247 nm was measured for each drug concentration. A Calibration curve relating trough amplitude to drug concentration in µg mL^{-1} was constructed, and the regression equation was derived.

Ratio derivative method

Different aliquots of trazodone hydrochloride standard solution(100 µg mL^{-1}) ranging from (10–300 µg) were transferred to 10-mL volumetric flasks and completed to volume with water. The absorption spectra (from 200 to 400 nm) of these solutions were recorded using water as a blank and then divided by the spectrum of trazodone hydrochloride degradation solution (10 µg mL^{-1}).The second derivative corresponding to each ratio spectrum was recorded, using $\Delta\lambda$ = 10 nm. The amplitude values were measured at 232 nm.

Ratio difference method

Aliquots equivalent to (10 – 300 µg) were accurately transferred from trazodone hydrochloride standard working solution (100 µg mL^{-1}) into a series of 10- mL volumetric flasks then completed to volume with water. The absorption spectra of the prepared standard solutions are scanned from 200 - 400 nm and stored in the computer.

The stored spectra of trazodone hydrochloride are divided by the absorption spectrum of (10 µg mL^{-1}) of the alkaline degradation product to get the ratio spectra. The amplitude difference at 238.0 and 259.0 nm (ΔP238.0 – 259.0) was plotted against the corresponding trazodone hydrochloride concentration in µg $mL^{-1,}$ and the regression equation was computed.

Mean centering method

Aliquots equivalent to (10– 300 µg) of trazodone hydrochloride working standard solution (100 µg mL^{-1}) were accurately transferred into a series of 10 - mL volumetric flasks then completed to volume with water. The absorption spectra of the prepared standard solutions were scanned from 200 - 400 nm using water as a blank and stored in the computer. The absorption spectra of trazodone hydrochloride were divided by the spectrum of (10 µg mL^{-1}) of its degradation product to get the ratio spectra then mean centered and the amplitude of the mean centered peak was measured at 238 nm. A calibration graph relating the peak amplitude to the corresponding concentrations in µg ml^{-1} of trazodone hydrochloride was constructed.

Bivariate method

Different aliquots equivalent to (10–300) µg of trazodone hydrochloride and (50–400) µg of its alkaline degradation product were accurately transferred from their standard solutions (100 µg mL^{-1}) into two separate series of 10-mL volumetric flasks and completed to volume with water. The absorption spectra (from 200 to 400 nm) of these solutions were recorded using water as a blank. The absorbance was measured at 242 and 262 nm and then the corresponding regression equations were determined at the selected wavelengths for both components.

Dual wavelength method

Aliquots of standard trazodone hydrochloride solution (100 µg mL^{-1}) containing (10 – 300) µg of the drug were added to a series of 10-ml volumetric flasks and then diluted to the mark with water. The absorption spectra (from 200 to 400 nm) of these solutions were recorded using methanol as a blank. The difference in the absorbance was measured at 230 and 247 nm and then plotted against the corresponding drug concentration in µg mL^{-1} to obtain the calibration curve

Analysis of Pharmaceutical Preparation

Ten Trittico ® tablets were accurately weighed and finely powdered, then a quantity equivalent to 100 mg of trazodone hydrochloride was shaken three times with 25 mL of water for 15 minutes then filtered into 100 -mL volumetric flask and the volume was adjusted to the mark with water to obtain a concentration of (100µg mL^{-1}). The solution was analyzed using the procedure described under the proposed methods.

RESULTS AND DISCUSSION

Spectral Characteristics

The zero order (D_0) absorption spectra of trazodone hydrochloride (10 µg mL^{-1}) and its alkaline degradation product (10 µg mL^{-1}) were recorded against water as blank over the range of 200 – 400 nm **(Figure 2)**.

Confirmation of complete degradation

Complete degradation product was checked by TLC on silica gel 60 GF254 plates using mobile phase consists of (chloroform, methanol and ammonia) (40: 20:0.5 v/v).It was confirmed by absence of spot in the region of degradate corresponds to spot of intact drug.

Second derivative method

[23-26] It is clear from the spectra in (Figure 2) that, there is a band overlapping between the drug and its alkaline degradation product. Such overlapping can be eliminated by obtaining the second derivative (^2D) of the absorption spectra trazodone hydrochloride and its degradation product in water, trazodone hydrochloride has a trough at 247 nm which shows no interference from the degradation product. Thus it would be possible to adopt the (^2D) spectrophotometry at 247 nm for direct determination of trazodone hydrochloride in presence of its degradation product as seen in (Figure 3).

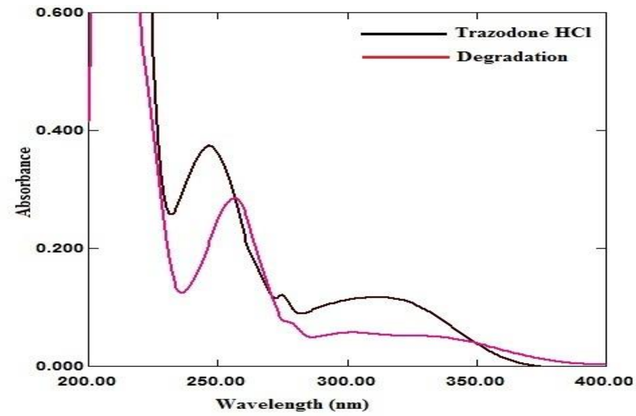


Fig.2: Zero-order absorption spectra of intact trazodone hydrochloride (10µg ml^{-1}) and its alkaline degradation product (10 µg ml^{-1}) in water.

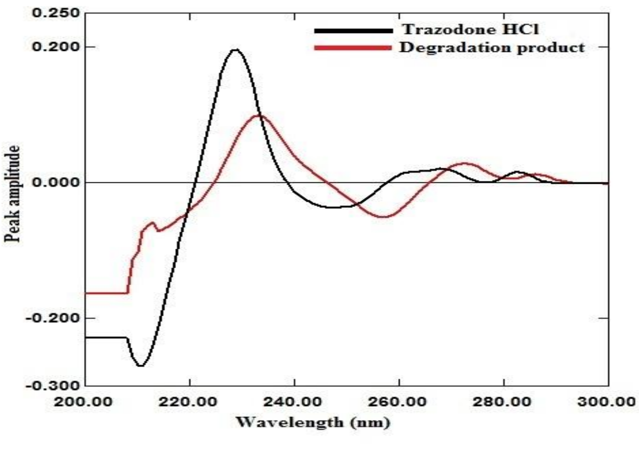


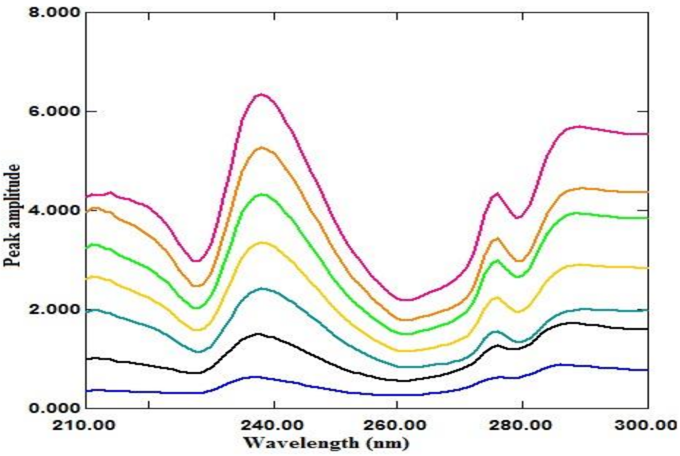
Fig.3: Second-derivative spectra of intact trazodone hydrochloride (10 µg ml^{-1}) and its alkaline degradation product (10 µg ml^{-1}) in water.

Ratio derivative method

Salinas et al.[27] designed a spectrophotometric method, which is based on the derivation of the ratio spectra for resolving binary mixtures. The main advantage of the ratio spectra derivative spectrophotometry is the chance of doing easy calculations in correspondence of peaks so it permits the use of the wavelength of the highest value of analytical signals (a maximum or a minimum) [28-30]. Moreover, the presence of a lot of maxima and minima is another advantage by the fact that these wavelengths give an opportunity for the determination of active compounds in the presence of excipients and other compounds which possibly interfere the assay. In this method, the absorption spectrum of the mixture is divided by the absorption spectrum of a standard solution of one of the components, then the derivation of this ratio to obtain the first derivative of the ratio spectrum. The concentration of the component of interest is then determined from a calibration graph.

The main parameters that improve the shape and the signal-to-noise ratio spectra are scanning speed, wavelength and the concentration of the standard solution used as a divisor; through the derivative obtaining, both the wavelength increment ($\Delta\lambda$) and the smoothing function are carefully tested. The ratio spectra presented in (Figure 4) and the first derivative of the ratio spectra presented in (Figure 5) may provide a good proof for this understanding. The effect of wavelength scanning speed is studied. Medium scanning speed is chosen to perform measurements as at low scanning speed, the noise was decreased but a longer time is needed for the measurement while at noisy high-speed spectra were obtained, different concentrations of divisor are used to study divisor concentration effect (5, 10 and 20 µg mL^{-1}) of trazodone hydrochloride degradation product and the divisor of concentration 10 µg ml^{-1} is found to be the best regarding average recovery.

The absorption spectra of trazodone hydrochloride were divided by the absorption spectrum of 10 µg ml^{-1} trazodone hydrochloride degradation product and smoothed (Figure 4) for determination of trazodone hydrochloride in the presence of its degradation. This gave the best compromise regarding sensitivity, repeatability, and signals to noise ratio. The choice of wavelength for the measurement was carefully studied. The trough amplitude at 232 and 249.0 nm and peak amplitude at 270 nm of the first derivative of ratio spectra are then stored respectively. Good linearity at each one was



observed, but the recovery percent at 232.0 nm was better, which may be related to its higher signal to noise ratio.

Figure.4: Smoothed ratio spectra of trazodone hydrochloride(1-30µgml^{-1}) using (10 µgml^{-1}) trazodone Degradation product as the divisor.

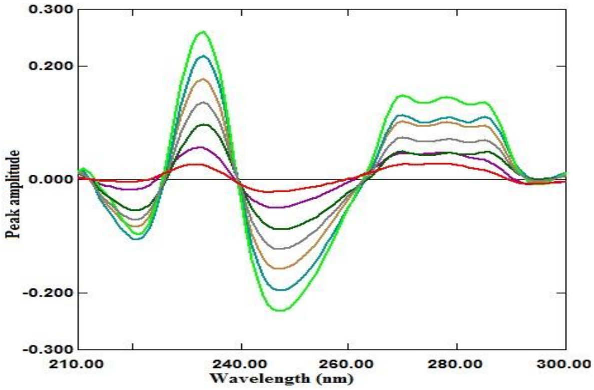


Fig.5: First derivative of smoothed ratio spectra of trazodone hydrochloride (1– 30) µg ml^{-1}) using (10 µgml^{-1}) trazodone hydrochloride degradation product as the divisor.

Ratio difference method

Ratio difference [31] is a new simple, rapid, selective method for the simultaneous determination of components having severe overlapping spectra in binary mixtures, having the advantages of minimal data processing and a wider range of application. The binary mixture of trazodone hydrochloride and its alkaline degradation product was chosen as an example for the application of the innovative ratio difference method.

The absorption spectra of trazodone hydrochloride and its degradation product show a certain degree of interference as shown in (Figure 2), that the application of direct spectrophotometry failed to determine trazodone hydrochloride in the presence of its degradation product.

Several approaches have been developed to eliminate the overlapping constant in the ratio spectrum, either using certain order derivative or through a sophisticated subtraction [32]; the later was capable of determining only the component with the less extended spectrum in the mixture. The ratio difference method is a simple modern method was capable of determining trazodone hydrochloride in the presence of its alkaline degradation product with minimal data processing, high selectivity.

The method includes two essential steps, the first is the selecting of the divisor, and the selected divisor should compromise between minimal noise and maximum sensitivity. Different concentrations of divisors are used (5, 10 and 20µg ml^{-1}) of the degradation and the divisor concentration 10 µg $mL^{-1}$was found the best regarding average recovery percent when it was used for the prediction of trazodone hydrochloride concentration in bulk powder as well as in laboratory prepared mixtures.

The second important step is the selection of the wavelengths at which measurements are performed. Any two wavelengths can be chosen provided that they display different amplitudes in the ratio spectrum and a good linearity is obtained at each wavelength individually. The linear correlation was obtained between the differences in amplitudes at 238.0 and 259.0nm, against the corresponding concentration of trazodone hydrochloride.

Mean centering method

In this method [27], the absorption spectra of the drug were divided by a convenient absorption spectrum of the interfering drug (divisor) to get the ratio spectra figure (4). The best divisor concentration was 10 µg/ml of its degradation product. The obtained ratio spectra were mean centered using MATLAB, and the concentration of trazodone hydrochloride was determined by measuring the amplitude at 238 nm.

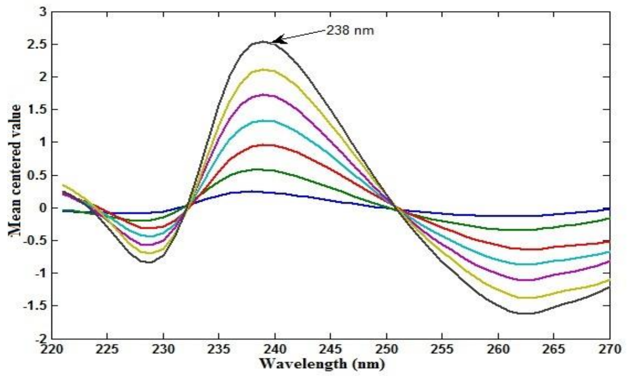


Fig.6: Mean centered ratio spectra of trazodone hydrochloride (1 – 30 μg ml^{-1}) Using (10 μg ml^{-1}) of trazodone degradation product as a divisor.

Bivariate method

The bivariate spectrophotometric method has been developed for the resolution of binary mixtures. To apply the bivariate method in the resolution of trazodone hydrochloride in mixture with its alkaline degradation product, the absorbance of the two components at several different selected wavelengths was recorded in the region of overlapping; from 232 to 262 nm at 5 nm interval. The calibration curve equations and their respective linear regression coefficients were obtained directly with the aim of confirming that there was a linear relationship between the absorbance and the corresponding concentration. All of the calibration curves at the selected wavelengths showed a satisfactory linear regression coefficient (r^2> 0.9988). According to Kaiser Method [33], at the chosen wavelengths, the slope values of the linear regression equations for both trazodone hydrochloride and trazodone hydrochloride degradation product were used to calculate the sensitivity matrices K to choose the optimum pair of the wavelength at which the binary mixtures were recorded as shown in table (1).

Table 1: Values of the sensitivity matrix determinates calculated according to Kaiser's method (k x 10^{-6}) for the mixture of trazodone hydrochloride and its alkaline degradation product by the proposed bivariate method

λ/λ	232	237	242	247	252	257	262
232	0	-91.19	-92.3	-26.9	80.76	112.31	179.22
237		0	17.21	99.96	214.29	249.26	277.38
242			0	96.1	232.14	273.49	**314.58**
247				0	151.74	196.64	278.28
252					0	43.17	175.5
257						0	148.26
262							0

$$K = \begin{bmatrix} m_{A_1} & m_{B_1} \\ m_{A_2} & m_{B_2} \end{bmatrix}$$

For the bivariate determination of trazodone hydrochloride in mixture with its alkaline degradation product. 242and 262 nm were found to give the maximum value of K and thus can be used for the analysis.

Dual wavelength method

The utility of dual wavelength [34] method is to calculate the unknown concentration of a component of interest present in a mixture containing both the components of concern and the interfering component by the mechanism of the absorbance difference between two points on the mixture spectra where the absorbance for alkaline degradation product was the same at the selected two wavelengths. The calibration curves were prepared by plotting absorbance difference of two wavelengths (230 nm – 247 nm). The response for the trazodone hydrochloride was found to be linear in the concentration range 1 - 30 μg mL^{-1}and at absorbance difference at the two wavelengths (230 nm – 247 nm) and the corresponding drug concentration

VALIDATION OF THE METHODS

Linearity

Second derivative method

At the described wavelength linear relationship was obtained between the trough amplitude and the trazodone hydrochloride concentration in the range of (1 - 30 μg mL^{-1}). The linear regression equation of the method was:

$$A_{247} = 0.0034\,C + 0.0032 \qquad (r = 0.9998)$$

Where **A** is an amplitude of the second derivative at 247 in cm and **C** is the drug concentration in μg mL^{-1}and **r** is the correlation coefficient.

Ratio derivative method

Under the described experimental conditions, the calibration graph for the method was constructed by plotting trough amplitude of the first derivative of the ratio spectra at 232 nm versus concentration of μg/ml. The regression plot was found to be linear over the range of 1-30 μg mL^{-1}. The linear regression equation for the graph was:

$$P_{232} = 0.0079\,C + 0.0168 \qquad (r = 0.9996)$$

Where C is the concentration of trazodone hydrochloride in μg mL^{-1}, P is the trough amplitude of the first derivative of the ratio spectrum curve at 232 nm and r is the correlation coefficient.

Ratio difference method

Linear correlation was obtained between the differences in amplitudes at 238.0 and 259.0nm of the ratio spectra against the corresponding concentration of trazodone hydrochloride. Good linearity is obtained in the concentration range of 1 - 30 μg mL^{-1}. The corresponding regression equation was computed to be:

$$\Delta P_{238.0-259.0} = 0.125\,C + 0.2651 \qquad (r = 0.9998)$$

Where ∆P is the amplitude difference at the selected wavelengths of the ratio spectra, C is the concentration in μg mL^{-1} and r = the correlation coefficient.

Mean centering method

Linear correlation was obtained between the mean-centered values of the ratio spectra at 238 nm, against the corresponding concentration of trazodone hydrochloride. Good linearity is obtained in the concentration range of (1 - 30 μg mL^{-1}). The corresponding regression equation was computed to be:

$$MCN_{238} = 0.0764\,C + 0.17 \qquad (r = 0.9995)$$

Where MCN is the peak amplitude of the mean centered ratio spectrum curve, C is the concentration in μg ml^{-1} and r is the correlation coefficient.

Bivariate method

At the described wavelengths linear relationship was obtained between the absorbance and the corresponding concentration of trazodone hydrochloride. Good linearity is obtained in the concentration range of (1 - 30 μg mL^{-1}) trazodone hydrochloride. The corresponding regression equation was computed to be:

$A_{242} = 0.0283\ C + 0.0637$ (r = 0.9997)

$A_{262} = 0.0156\ C + 0.0478$ (r = 0.9995)

Where A is the absorbance at selected wavelength, C is the concentration in µg mL^{-1} and r = the correlation coefficient.

Dual wavelength method

The calibration curves were plotted over a concentration range of 1 - 30 µg mL^{-1} for trazodone hydrochloride.

$\Delta P_{230.0-247.0} = 0.0085\ C + 0.0047$ (r = 0.9997)

Where ∆P is the absorbance difference at the selected wavelengths, C is the concentration in µg mL^{-1} and r = the correlation coefficient.

LOD and LOQ

The limit of detection (LOD) and the limit of quantitation (LOQ) were calculated according to ICH Q_2 Recommendation [35] from the following equations:

$LOD = 3.3\ S_a$ / slope

$LOQ = 10\ S_a$ / slope

Where S_a is the standard deviation of the intercept of the regression line.

Results presented in Table 2, indicated that the method is sensitive for determination of the studied drugs.

Accuracy and precision

Accuracy and precision of the method were determined by applying the proposed procedure for determination of three different concentrations, each in triplicate, of trazodone hydrochloride in pure form within linearity range in the same day (intraday) and on three successive days (interday).Accuracy as percent recovery (R %) and precision as percent relative standard deviation (RSD %) were calculated and results are listed in table 2.

Specificity

The specificity of the proposed procedure was assured by applying it to laboratory prepared mixtures of the intact drug with its alkaline degradation product. The proposed procedure was adopted for the selective determination of intact trazodone hydrochloride in presence of up to 80.00 % of its degradation product. The percentage recovery±%RSD was shown in Table 3.

Statistical analysis

Results obtained by the developed methods for the determination of trazodone hydrochloride in Trittico tablets were statistically compared with those obtained by applying the reported method [2]. The calculated t- and F-values were found to be less than the theoretical ones, confirming no significant differences [36], as shown in Table 4.

Another statistical comparison of the obtained results by the proposed methods and the reported method for the determination of trazodone hydrochloride in pharmaceutical products using one-way ANOVA test was shown in Table 5. The results obtained by applying these methods show no significant differences between all of them. Moreover, the developed methods have the advantage of being more simple, rapid and economic over the reported ones.

Table 2. Validation parameters for determination of trazodone hydrochloride the proposed spectrophotometric methods.

Parameters	Second derivative	Ratio derivative	Ratio difference	Mean centering	bivariate		Dual wavelength
wavelength (nm)	247	232	238-259	238	242	262	230-247
Linearity range (µgml^{-1})	1-30	1-30	1-30	1-30	1-30	1-30	1-30
LOD (µgml^{-1})	0.208	0.347	0.265	0.116	0.249	0.252	0.199
LOQ (µgml^{-1})	0.630	1.054	0.805	0.351	0.754	0.763	0.603
Regression equations							
Slope	0.0034	0.0079	0.125	0.0764	0.0283	0.0156	0.0085
Intercept	0.0032	0.0168	0.265	0.173	0.0637	0.0478	0.0047
Correlation Coefficient (*r*)	0.9998	0.9996	0.9998	0.9995	0.9997	0.9995	0.9997
Accuracy (**%recovery mean±S.D.**)	99.93±0.699	98.76±0.685	100.18±0.428	99.90±0.645	100.42±1.050		100.63±0.648
Precision(%RSD)							
Repeatability[c]	0.700	0.693	0.427	0.645	0.671	0.864	0.645
Intermediate precision	0.833	0.787	0.655	0.637	0.545	0.654	0.292

[c]The interday (n = 3), average of three different concentrations repeated three times in three successive days.

Table 3: Determination of trazodone hydrochloride in presence of its alkaline degradation product in their laboratory mixtures by the proposed methods.

Method	Intact (µg ml^{-1})	Degradation product (µg ml^{-1})	% degradation product	%Recovery of intact
Second derivative	24	6	20.00%	99.14
	20	10	33.33%	98.68
	16	14	53.33%	98.90
	12	18	60.00%	100.49
	6	24	80.00%	100.98
	Mean ± %RSD			**99.64±1.034**
Ratio derivative	24	6	20.00%	100.84
	20	10	33.33%	98.86
	16	14	53.33%	99.05
	12	18	60.00%	101.48
	6	24	80.00%	101.69
	Mean ± %RSD			**100.38±1.336**
Ratio difference	24	6	20.00%	101.03
	20	10	33.33%	99.48
	16	14	53.33%	98.5
	12	18	60.00%	101.53
	6	24	80.00%	98.12
	Mean ± %RSD			**99.73±1.512**

Mean centering	24	6	20.00%	100.30
	20	10	33.33%	99.61
	16	14	53.33%	100.55
	12	18	60.00%	99.24
	6	24	80.00%	101.39
	Mean ± %RSD			**100.22±0. 837**
bivariate	24	6	20.00%	99.71
	20	10	33.33%	99.00
	16	14	53.33%	99.14
	12	18	60.00%	99.58
	6	24	80.00%	100.17
	Mean ± %RSD			**99.52±0.468**
Dual wavelength	24	6	20.00%	101.76
	20	10	33.33%	98.23
	14	16	53.33%	99.92
	12	18	60.00%	100.19
	6	24	80.00%	100.39
	Mean ± %RSD			**100.10±1. 260**

Table 4: Determination of trazodone hydrochloride in Trittico ® 50 mg tablets by the proposed and reported methods .

	Second derivative	Ratio derivative	Ratio difference	Mean centering	bivariate	Dual wavelength	Reported method(2)
n*	5	5	5	5	5	5	5
X̄	99.60	99.63	98.78	99.67	100.42	99.97	99.14
SD	1.107	0.685	0.785	0.712	1.050	1.588	0.736
RSD%	1.111	0.688	0.795	0.714	1.045	1.589	0.742
t*	0.777 (2.306)	1.086 (2.306)	1.170 (2.306)	0.703 (2.306)	2.242 (2.306)	1.069 (2.306)	——
F***	2.263 (6.388)	1.152 (6.388)	1.139 (6.388)	1.068 (6.388)	2.036 (6.388)	4.659 (6.388)	——

*** Number of experiments, ** The mean of percent recovery of pharmaceutical preparation' *** The values in parenthesis are tabulated values of "t "and "F" at (P = 0.05).**

Table 5:One-way ANOVA testing for the different proposed methods used for the determination of trazodone hydrochloride in trittico® tablets.

Drug	Source	DF	Sum of squares	Mean square	*F* value
trazodone	Between exp.	5	3.078	0.615	0.572
	Within exp.	24	25.79	1.074	(2.620)

CONCLUSION

The proposed methods are simple, rapid and inexpensive. So, it is a good alternative to the other few reported methods and to the high-cost HPLC methods. The developed chemometric methods have the advantages of being simpler and not expensive over the chromatographic method.

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