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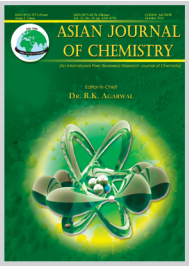

Visible Spectrophotometric Methods for the Determination of Naratriptan Hydrochloride in Pure and Dosage Forms

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Two simple, sensitive and reproducible visible spectrophotometric methods are developed for the determination of naratriptan hydrochloride in pure and its dosage forms. Method-A (brucine/periodate) is based on the nucleophilic attack of bruciquinone on secondary nitrogen atom of substituted indole ring of the drug to give 1-monosubstituted bruciquinone derivative. In method-B (isatin/sulfuric acid) one mole of the lactam tautomeric form of the isatin condenses with secondary amine group in substituted indole ring of the drug in presence of concentrated sulphuric acid with the elimination of one mole of water. The absorption maximum and molar extinction coefficient are found to be 530 nm, 2.88×10^3 and 560 nm, 6.72×10^3 for method-A and method-B respectively. The developed methods are linear within the limits 12.5-70.0 µg/mL and 8.0-48.0 µg/mL with correlation coefficient 0.9998 and 0.9991. These methods are precise, accurate and reproducible. The results of analysis are validated statistically and by recovery studies.

Key Words: Naratriptan hydrochloride, Brucine, Isatin, Linearity, Correlation coefficient and recover.

INTRODUCTION

Naratriptan is chemically known as *N*-methyl-3-(1-methyl-4-piperidinyl)-1*H*-indole-5-ethanesulfonamide mono hydrochloride. It is a novel second generation triptan anti-migrane used for the treatment of the acute migraine attacks and the symptoms of migraine, including severe, throbbing headaches that sometimes are accompanied by nausea and sensitivity to sound or light[1,2]. Its molecular formula and molecular weight are $C_{17}H_{25}N_3O_2S$. HCl and 371.93 g/mol respectively. It appears as white powder and soluble in cold water and methanol. Pharmaceutical formulations are Naratrex (Sun Pharma, 1.0 mg Table), Amerge (Glaxo Smith Kline, 1.0 mg Tablet), Naramig (Glaxo Smith Kline, 2.5 mg Tablet). Each tablet contains the inactive ingredients such as croscarmellose sodium; hypromellose; lactose; magnesium stearate; micro-crystalline cellulose; triacetin; and titanium dioxide, iron oxide yellow (2.5 mg tablet only) and indigo carmine aluminum lake (FD and C Blue No. 2) (2.5-mg tablet only) for colouring.

An extensive literature survey is carried out and it is evident that a few chromatographic methods are reported in the literature for the determination of naratriptan in biological matrices. Dulery *et al.*[3] have developed a liquid chromatographic electro spray mass spectrometric assay for the determination of naratriptan, sumatriptan in rabbit plasma. Vishwanathan and co workers[4] have reported a rapid, sensitive and selective LC-ESIMS/MS method for the determination of antimigran drugs such as naratriptan, sumatriptan and rizatriptan in human serum. Yadav *et al.*[5] have reported a LC-ESI-MS/MS method for the quantification of naratriptan in human plasma using sumatriptan as internal standard. Some visible spectrophotometric methods[6,7] have been reported to determine naratriptan in pure and formulations. A volatametric method is also reported for the determination of naratriptan by Velasco and Alvarez[8]. The reported chromatographic methods are applied in biological fluids only. The analytically useful functional groups present in naratriptan have not been fully exploited for designing suitable visible spectrophotometric methods and therefore offer a scope to develop more number of new visible spectrophotometric methods with better sensitivity, selectivity, precision and accuracy. The author has made some attempts in this direction and succeeded in developing new visible spectrophotometric methods.

EXPERIMENTAL

UV-Visible spectrophotometer: An Elico-SL159 model, 2 nm high resolution, double beam, 1 cm length quartz coated optics and wavelength range 190-1100 nm is used for all the spectral measurements.

Precision balance: 0.001 g Readability, 200 g capacity, 0.001g repeatability, 0.002 g linearity balance is used to weigh the required amount of the drug and the reagents.

Standard solution of naratriptan hydrochloride: Stock solution of naratriptan hydrochloride (1 mg/1 mL) is freshly prepared by transferring accurately weighed 100 mg of naratriptan hydrochloride into 100 mL volumetric flask and dissolved in double distilled water and then made up to the mark. Working standard solutions 250 µg/mL and 200 µg/mL are prepared by transferring 25 mL and 20 mL of the stock solution into two 100 mL standard flasks respectively and made up to the mark. 250 µg/mL working standard solution was used for method-A (Brucine/Periodate) and 200 µg/mL working standard solution was used for method-B (isatin/ sulfuric acid).

Brucine solution (Loba; 0.2 %, 5.067 × 10^{-3} M, w/v): 200 mg of brucine is accurately weighed, transferred into 100 mL volumetric flask and dissolved 2 mL of H_2SO_4 and then diluted to 100 mL with distilled water.

$NaIO_4$ solution (BDH; 0.2 %, 9.35 × 10^{-3} M, w/v): 200 mg of sodium meta periodate is accurately weighed, transferred into 100 mL volumetric flask, made up to the mark with distilled water.

Isatin solution (Sd Fine) 0.04 %, 2.718 × 10^{-2} M, w/v): Prepared by dissolving 40 mg of Isatin in 100 mL of CH_3COOH.

Method-A: Different aliquots of naratriptan solution are transferred into different 10 mL graduated tubes. 3.0 mL of 0.2 % (5.067 × 10^{-3} M) of brucine solution, 2.0 mL (9.35 × 10^{-3} M) of sodium metaperiodate solution and 2.0 mL (2.3 M) of sulphuric acid are added to each tube and the total volume is made up to 9 mL with distilled water. The tubes are thoroughly shaken and placed in a boiling water bath for 15 min. The reaction mixture is then cooled to room temperature and total volume is adjusted to 10 mL with distilled water. The absorbance of the standard is scanned from the wavelength 350 to 800 nm against a similar reagent blank and found that the maximum absorption (λ_{max}) 530 nm. The absorbance of each solution is measured at 530 nm against a reagent blank. The calibration curve is drawn by plotting absorbance against weight of the drug in µg/mL. The amount of naratriptan present in the solution is determined from the calibration graph.

Methods-B: Aliquots of naratriptan solution are transferred into different 25 mL graduated tubes and the volume of the each test tube is adjusted to 3 mL with methanol. To each of these tubes 3 mL of 2.718 × 10^{-3} M isatin and 3.0 mL of sulphuric acid are added by thoroughly shaking. The reaction mixture is then cooled to room temperature and total volume is adjusted to 25 mL with methanol. Then the absorbance of the standard is scanned from the wavelength 350 to 800 nm against a similar reagent blank and maximum absorption is found to be 560 nm. The absorbences of the different standard solutions are measured at 560 nm against a similar reagent blank. The amount of naratriptan is calculated from the calibration curve which is drawn absorbance against weight of the drug in µg/mL.

Assay of pharmaceutical formulations: Tablet formulations are powdered and mixed thoroughly. An amount of the powder equivalent to 100 mg of the drug is accurately weighed, dissolved in methanol, shaken well, filtered and the filtrate is made up to 100 mL with triple distilled water. 25 mL and 20 mL of this solution are further diluted to 100 mL to obtain working standard solutions of 250 µg/mL, 200 µg/mL respectively. The percent recoveries are determined by adding different known amounts of the standard drug to equal amount of test sample. Commercial formulations of naratriptan hydrochloride are successfully analyzed by the proposed methods. The values obtained by the proposed and reference methods for the formulations are compared statistically with F-test and t-test and found to be not different significantly.

RESULTS AND DISCUSSION

In order to ascertain the optimum wavelength of maximum absorption (λ_{max}) of the coloured species formed in both methods specified amount of naratriptan is taken and colour has been developed. The absorption spectrum is scanned on a spectrophotometer in the region of 380 to 900 nm against similar reagent blank. The reagent blank absorption spectrum of each method is also recorded against distilled water. The absorption curves are drawn by plotting wavelength against absorbance. The absorption curves of the coloured species in each method show characteristics absorption maxima, where as the blank in each method has low or no absorption in this region. In order to test whether the coloured species formed in these methods adhere to Beer's law or not a series of working standard solutions containing varying amounts of naratriptan HCl are taken, specified amount of reagents are added, made up to the mark, shaken well and measured the absorbance against the corresponding reagent blank at maximum wave length. Beer's law plots are drawn by taking weight of the drug (µg/mL) on X-axis versus absorbance on y axis. Beer's law limits, Molar absorptivity, Sandell's sensitivity and optimum photometric range in each method are calculated (Table-1). Linear least square regression analysis is carried out for getting the slope, intercept and correlation coefficient values (Table-2).

TABLE-1
OPTICAL CHARACTERISTICS FOR THE PROPOSED METHODS

Name of the parameter	Method-A	Method-B
Maximum wavelength λ_{max}	530 nm	560 nm
Beer's law limits (µg/mL)	12.5-70.0	8.0-48.0
Optimum photometric range (µg/mL)	25-62.5	16.032.0
Molar absorptivity (L/mol/cm)	2.88E+03	6.72E+03
Sandell's sensitivity (µg/cm^2 / 0.001 Abs)	1.21E-01	5.19E-02

TABLE-2
LINEAR LEAST SQUARE REGRESSION ANALYSIS

Name of the oarameter	Method-A	Method-B
Slope (b)	7.73E-03	1.81E-02
Intercept(a)	1.03E-02	2.29E-02
Standard deviation on slope (S_b)	9.17E-05	3.88E-04
Standard deviation on intercept (S_a)	4.47E-03	1.21E-02
Correlation coefficient (r)	0.9998	0.9991
Limit of detection (µg/mL)	1.732	2.090
Limit of quantification (µg/mL)	5.774	6.695

The precision of each method is determined by measuring the absorbance of six replicate concentrations of naratriptan hydrochloride (50 µg/mL for the method method-A and 32 µg/mL for method method-B). The low per cent of relative standard deviation values show that these methods are precise. High per cent of recovery of the drug at different concentration

levels indicates that the developed methods are accurate (Tables 3 and 4). Commercial formulations of the drug are successfully analyzed by these methods. The % RSD and % recovery values obtained by the proposed are compared with reference method by applying statistical tests such as F-test and *t*-test. These methods are found to be not significantly different. The limit of detection and limit of quantification of the developed methods are evaluated based on the standard deviation of the intercept (Sa) and slope of calibration curve (b) (Table-5).

TABLE-3
PRECISION OF THE PROPOSED METHODS

Name of the parameter	Method-A	Method-B
Amount taken (µg/mL)	50.00	32.00
Amount found (µg/mL)	49.99	32.07
Standard deviation (S)	0.419	0.273
Relative standard deviation (%)	0.837	0.852
Recovery (%)	99.98	100.20
0.05 CI	0.335	0.219

TABLE-4
ACCURACY OF THE PROPOSED METHODS

Amount taken (µg/mL)	Amount found[a] (µg/mL)	Percent of recovery	SD	RSD (%)
Method-A				
37.50	37.47	99.93	0.414	0.415
50.00	50.16	100.33	0.702	0.700
62.50	62.10	99.36	0.973	0.980
Method-B				
24.0	23.90	99.50	1.502	1.509
32.0	31.83	99.48	2.018	2.092
40.0	39.73	99.33	1.283	1.292

[a]Average of three determinations

Nature of the coloured species

Method-A: Sodium periodate is a powerful oxidizing agent generally used in oxidation of organic compounds. The dimethoxy benzene nucleus of brucine is attacked by IO_4^- with the formation of o-quinine (bruciquinone), which in turn undergoes nucleophilic attack on the most electron rich portion of the coupler *i.e.* secondary nitrogen atom of substituted indole ring of the drug to give 1-monosubstituted bruciquinone derivative.

Method-B: Naratriptan possesses a secondary amine group in substituted indole ring. Two isomeric forms exbited by Isatin are known as lactam-lactim tautomeric forms. One mole of the lactim tatomeric form of the isatin condenses with secondary amine group in substituted indole ring of one mole of drug in the presence of concentrated sulphuric acid with the elimination of one mole of water.

Conclusion

The proposed methods are simple, sensitive and reliable and can be used for routine analysis of Naratriptan pharmaceutical formulations. Results of the analysis of pharmaceutical formulations reveal that the proposed methods are suitable for their analysis with virtually no interference of the usual additives present in pharmaceutical formulations.

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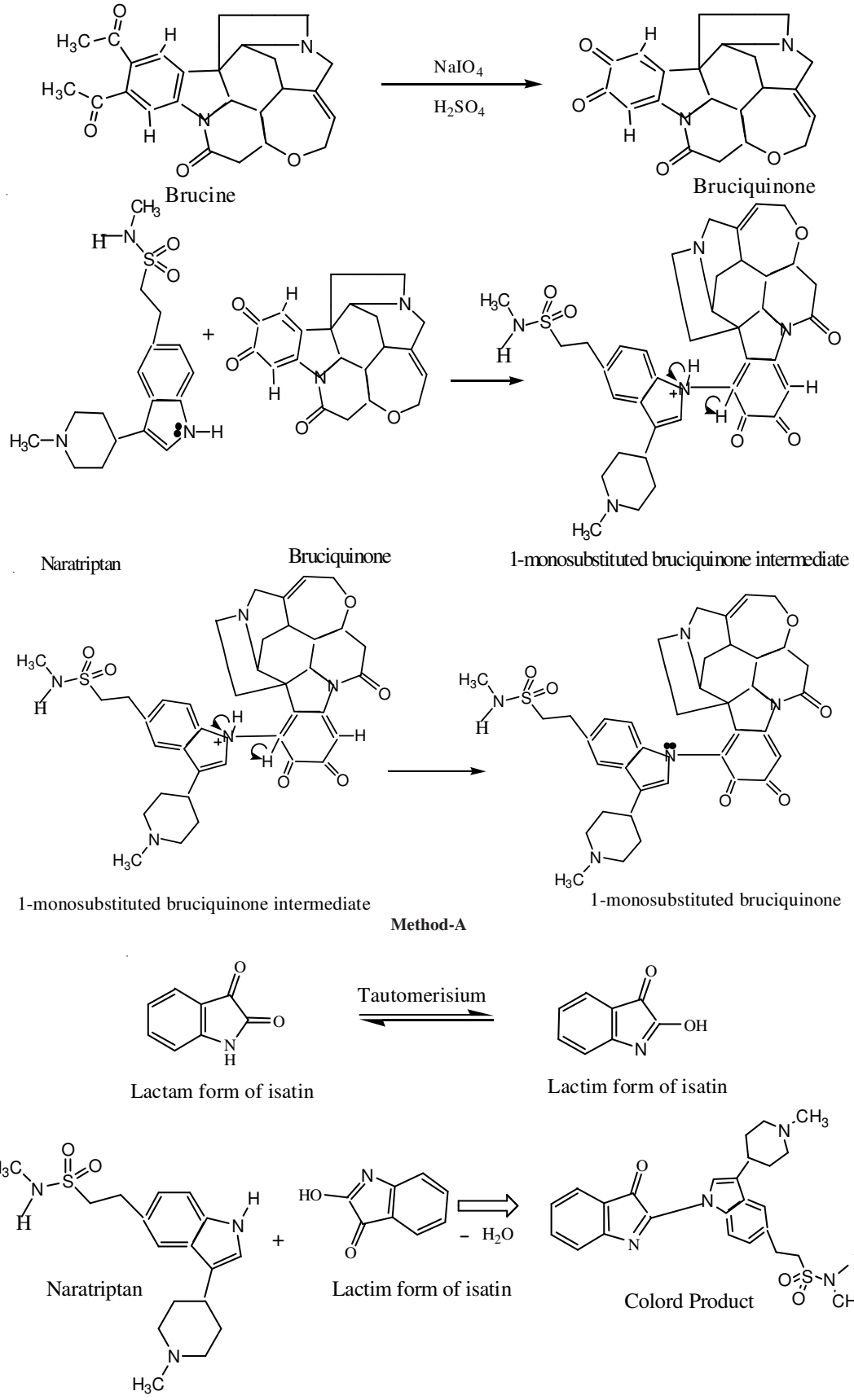
TABLE-5
ASSAY OF NARATRIPTAN IN PHARMACEUTICAL FORMULATIONS

Brand	Amount of the drug mg				Percent of recovery[b]			
	Taken	Found			Proposed methods			Reference
			Method-A	Method-B		Method-A	Method-B	M_{Ref}
Naratrex	2.5	Mean	2.498	2.478	REC (%)	99.93	99.91	100.4
		SD	±0.016	±0.016	RSD (%)	±0.632	±0.647	± 0.42
		F	2.263	2.371				
		t	0.093	0.028				
Naramig	2.5	Mean	2.497	2.503	REC (%)	99.90	100.11	99.6
		SD	± 0.017	± 0.020	RSD (%)	±0.680	±0.803	± 0.63
		F	2.619	3.666				
		t	0.081	0.567				
Naratrex	1.00	Mean	1.00	1.004	REC (%)	100.00	100.35	99.6
		SD	±0.009	±0.011	RSD (%)	±0.97	±1.108	± 0.63
		F	1.862	1.121				
		t	0.111	0.665				
Naramig	1.00	Mean	0.999	1.002	REC (%)	99.97	100.20	100.4
		SD	±0.002	±0.008	RSD (%)	±0.162	±0.784	± 0.42
		F	2.024	1.560				
		t	2.498	0.495				

[a]Average of six determinations are considered, AVG= average, SD= standard deviation, F= F-test value, t= t-test value; Theoretical values at 0.05 level of confidence limit F= 5.05, t= 1.812; [b] %REC= % of Recovery, % RSD= % of relative standard deviation; Recovery of 10.0 mg added to the preanalyzed formulations (Average of six determinations)



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