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Research Article

A New Spectrophotometric Method for the Estimation of Almotriptan Malate in Tablets Using Metol - Cr (VI) Reagent

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Abstract

A simple and sensitive visible spectrophotometric method has been developed for the estimation of almotriptan malate either in bulk or tablet dosage forms. The method involves charge-transfer complex formation at pH 3.0 with p-N methyl benzoquinone monoimine (*in situ* oxidation product of metol and oxidant Cr (VI) to form a purple colored species with an absorption maximum of 540nm. Beer's law obeyed in the concentration range of 20-100 µg/ml. No interference was observed from the usually existing additives in pharmaceutical formulations and the applicability of the method was examined by analyzing AXERT tablets containing AM. The statistical data indicates the accuracy, reproducibility and the precision of the proposed method.

Keywords: Beer's Law; Charge-Transfer Complex Formation; Regression Equation; Statistical Analysis; Tablets

Introduction

Almotriptan malate (AM) (Figure 1) is a selective and potent serotonin 5-hydroxy trytamine1B/1D (5-HT 1B/1D) receptor agonist. It is chemically designated as 1[[[3-[2-(Di methyl amine) ethyl]-1H-indol-5-yl] methyl] sulfonyl] pyrrolidine ± - hydroxy butanedioate [1] (1:1). Its empirical formula is $C_{17}H_{25}N_3O_2S.C_4H_6O_5$ representing molecular weight of 469.56. It is a white to slightly yellow crystalline powder that is soluble in water and sparingly soluble in methanol. Almotriptan is available in market as conventional tablets (AXERT).The drug is absorbed well orally, with an absolute bioavailability of around 70%. The drug is used to treat severe migraine headaches and vascular headaches; acute treatment of migraine attacks with or without aura. The drug binds with high affinity to 5-HT 1D, 5-HT 1B and 5-HT 1F receptors. Because of the particular distribution of the 5-HT 1B/1D receptors, almotriptan basically constricts the human meningeal arteries; therefore it has a limited effect on arteries supplying blood to the brain and little effect on cardiac and pulmonary vessels. Ameliorate migraine through selective constriction of certain intracranial blood vessels, inhibition of neuro peptide release and reduced transmission in trigeminal pain pathway.

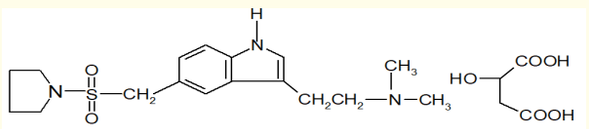

Figure 1: Chemical structure of Almotriptan malate.

In literature, several analytical methods such as HPLC [2-5], HPTLC [6], HPLC-MS/MS [7], LC-ESI-MS/MS [8], UV Spectrometric [9,10], Fluorometric and Coloricmetric [11], visible spectrophotometric [12-16] have been reported for the determination of AM in biological fluids and formulations. For routine analysis, simple, rapid and cost effective visible spectrophotometric methods are useful and preferred in small scale pharmaceutical industries. Nevertheless, there still exists a need for development of sensitive accurate and flexible visible spectrophotometric method for the determination of AM in pharmaceutical preparations and quality control analysis.

Metol is a versatile chromogenic reagent capable of reacting with different functional groups, enabling the estimation of many pharmacodynamic agents belonging to different classes [17-19]. So the authors have made some attempts in this direction and succeeded in developing a method. The proposed method is based on an observation that metol gives purple color with the drug at PH 3.0

in the presence of an oxidant Cr (VI) under specified experimental conditions.

The proposed method for AM determination has many advantages over other analytical methods due to its rapidity, normal cost and environmental safety. Unlike HPLC, HPTLC procedures, the instrument is simple and is not costly. Economically, all the analytical reagents are inexpensive and available in any analytical laboratory. The method can be extended for the routine quality control analysis of pharmaceutical products containing AM.

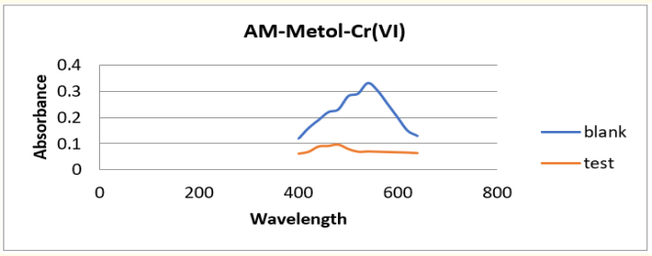

Figure 2: Absorption spectra of AM-metol-Cr (VI) system.

Materials and Methods (Experimental)

Apparatus and chemicals

A Milton Roy UV/Visible spectrophotometer model-1201 with 10mm matched quartz cells was used for all spectral measurements. A Systronics digital pH meter mode-361 was used for pH measurements. All the chemicals used were of analytical grade. AXERT tablets procured from Ortho Mc Nell Pharmaceuticals, USA.

PMAP (metol) solution (Wilson labs, 0.2%, 5.80x10-3M): prepared by dissolving 200mg of P-N-methyl amino phenol sulphate in 100ml of distilled water, Potassium dichromate solution (BDH 0.01M) was prepared in the usual way. H 3.0 Buffer solution: Prepared by adding 500ml of potassium acid phthalate solution (0.2M; 40.546g in 1lit.water) to 408ml of 0.1M HCl and the volume of mixture was brought to 2 lit. with distilled water and pH was adjusted to 3.0.

Preparation of standard drug stock solution

An accurately weighed quantity of 50mg pure AM drug was dissolved in little amount of acetic acid and made to 50ml with distilled water. The prepared stock solution was stored at 4^0C protected from light. This stock standard solution was further diluted stepwise with distilled water to obtain working standard solution and a series of standards were freshly prepared during the analysis day.

Determination of wavelength maximum (λ_{max})

A 5.0ml portion of the working standard solution of AM (500µg/ml) was accurate measured into 25 ml calibrated tube. 15ml pH 3.0 buffer solution, 1.0ml of 0.2% metol solution and 1.0 ml of 0.01M $K_2Cr_2O_7$ solution were added and mixed thoroughly. The solution was diluted to the mark with distilled water. In order to investigate the wavelength maximum, the above solution was scanned in the range of 350-750nm by UV-Visible spectrophotometer. From the spectra (Figure 2), it was concluded that 540nm is the most appropriate wavelength for analyzing AM with suitable sensitivity.

Analysis of Bulk samples

Aliquots of the standard AM drug solution ((1.0-5.0ml, 500µg/ml) were transferred into a series of 25ml calibrated tubes. 15ml of pH 3.0 buffer solution 1.0ml of 0.2% metol solution and 1.0 ml of 0.01M K2Cr2O7 solution were added and mixed thoroughly. The solution was diluted to the mark with distilled water and the absorbance were measured at 540 nm against a reagent blank prepared omitting drug solution in a similar manner during the stability period of 5min-2 hr. The amount of drug in a sample was calculated from its calibration curve (Figure 3).

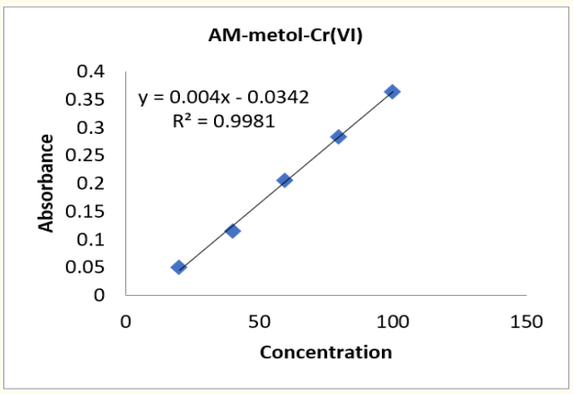

Figure 3: Beer's Law plot of AM-Metol-Cr (VI) system.

Analysis of tablets

Twenty tablets were weighed accurately and powdered and an amount of the tablet powder equivalent to 10mg of AM drug was treated with 8.0ml of glacial acetic acid (warmed on a boiling water-bath for 5 min with occasional shaking). The solution was cooled to room temperature, filtered and made up to 10ml with distilled water to give a solution of 1 mg/ml. This stock standard solution was further diluted stepwise with distilled water to obtain working standard solution and was analyzed as described in the analysis of bulk samples.

Results and Discussion

The optimum conditions for the development of the method was established by varying the parameters one at a time and keeping the others fixed and observing the effect produced on the absorbance of the colored species. Maintaining the pH of the solution at 3.0 ± 0.1 was found to be the best for attaining the maximum sensitivity. Use of 1.0 -2.0 ml of PMAP (metol) solution and 1.0 -2.0 ml of 0.01M $K_2Cr_2O_7$ solution afforded the maximum absorbance

values. A waiting period of 1-3 min was necessary between the additions of PMAP and $K_2Cr_2O_7$ solutions for the generation of p-N-methyl benzoquinone monoimine (PMBQMI) by the action of $K_2Cr_2O_7$ on PMAP. Prolonging the waiting period beyond 3 min resulted in low absorbance values, probably owing to the partial hydrolysis of the PMBQMI formed in situ to the quinone state. Among the water miscible solvents examined, water was found to be the best for final dilution of the solution. Maximum color intensity was attained within 10 min after the final dilution and remained stable up to 1 hr. The optical characteristics such as Beer's law limit, Sandell's sensitivity, molar absorptivity, percent relative standard deviation (calculated from the six measurements containing $3/4^{th}$ of the amount of the upper Beer's law limits) were calculated and the results are summarized in Table-1. Regression characteristics like standard deviation of slope (Sb), standard deviation of intercept (Sa), standard error of estimation (Se) and % range of error (0.05 and 0.01 confidence limits) were calculated and are shown in table 1.

AXERT tablets containing AM were successfully analyzed by the proposed method. The values obtained by the proposed and reference methods for formulations were compared statistically by the t-and F-test and found not to differ significantly. As an additional demonstration of accuracy, recovery experiments were performed by adding a fixed amount (10mg) of the drug to the pre analyzed formulations at three different concentration levels. These results are summarized in table 2. The interference studies in the determination of AM in pharmaceutical formulation revealed that the normally existing excipients and additives like starch, talc, stearic acid, boric acid, gelatin, magnesium carbonate and sodium lauryl sulphate were found not to interfere even when present in excess (1-100 folds). However, preliminary clean up procedure with $CHCl_3$ is necessary prior to the estimation of AM in formulations if lactose is present.

Parameter	Values
λ_{max} (nm)	540
Beer's law limit(µg/ml)	20-100
Sandell's sensitivity (µg/cm^2/0.001 abs. unit	0.011594203
Molar absorptivity (Litre/mole/cm)	40499.55
Correlation Coefficient	0.998
Regression equation (Y)*	
Intercept (a)	-0.038
Slope(b)	0.004
%RSD**	1.35
% Range of errors (95% Confidence limits)	
0.05 significance level	1.414
0.01 significance level	2.218

Table 1: Optical characteristics, precision and accuracy of proposed method.

*Y = a +b x, where Y is the absorbance and x is the concentration of AM in µg/ml

**calculated from six determinations

Method	*Formulations	Labeled Amount (mg)	Found by Proposed Method			Found by Reference Method ± SD	#% Recovery by Proposed Method ± SD
			**Amount found ± SD	t	F		
AM-metol-Cr(VI)	Tablet-1	12.5	12.43 ± 0.16	1.32	3.37	12.44 ± 0.15	98.42 ± 1.25

Table 2: Analysis of almotriptan malate in tablets.

*Tablet- 1 AXERT tablets of Ortho Mc Nell Pharmaceuticals, USA

**Average ± Standard deviation of six determinations, the t- and f-values refer to comparison of the proposed method with UV reference method. Theoretical values at 95% confidence limits t =2.57 and F = 5.05.

#Recovery of 10mg added to the pre analyzed sample (average of three determinations).

Reference method (reported UV method) using methanol (λ_{max}=227nm).

Chemistry of colored species

The cyclic imino group in indole portion of drug AM is involved in the formation of a colored species with situ oxidized form PMBQMI obtained from PMAP-Cr (VI). The probable sequences of reactions in two steps based on analogy are presented in figure 4.

Conclusion

The reagents utilized in the proposed method are normal cost, readily available and the procedure does not involve any critical reaction conditions or tedious sample preparation. The proposed method possesses reasonable precision, accuracy and is simple, sensitive and can be used as alternative method to the reported

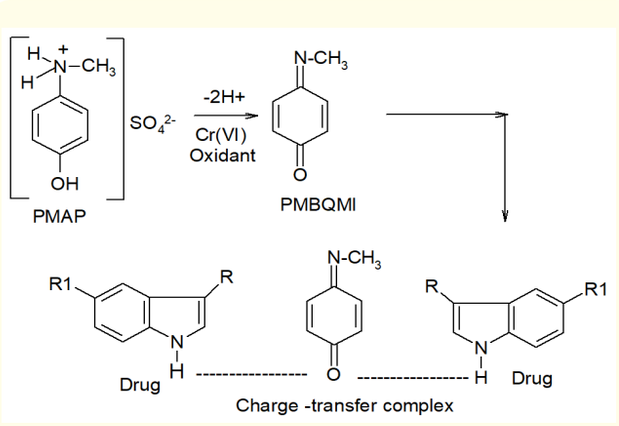

Figure 4: Probable sequence reactions of the proposed method.

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