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ASSAY OF ALMOTRIPTAN MALATE IN BULK AND PHARMACEUTICAL PREPARATIONS BY VISIBLE SPECTROPHOTOMETRY

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ABSTRACT

Two simple and sensitive visible spectrophotometric methods (A and B) have been developed for the determination of almotriptan malate in bulk and tablet dosage forms. Methods (A and B) are based on the reaction of drug with aromatic aldehydes such as Vanillin or Para dimethyl amino cinnamaldehyde (PDAC) in the presence of sulphuric acid in non aqueous medium and formed purple red colored condensation products with an absorption maximum of 560nm for method A and 565nm for method B. The Beer's law obeyed in the concentration range of 10-50µg/ml for method A and 20-60µg/ml for method B. The proposed methods are applied to commercial available tablets and the results are statistically compared with those obtained by the reference method and validated by recovery studies.

KEYWORDS: Almotriptan, Assay, PDAC, Regression analysis, Tablets, Vanillin, Visible spectrometry.

INTRODUCTION

Almotriptan malate (AM) (Figure1) 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.

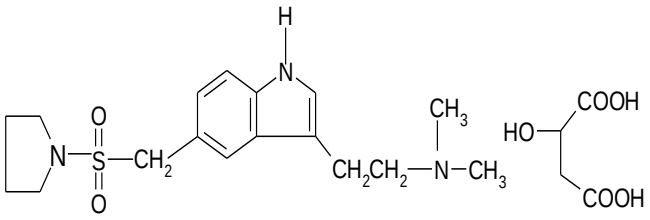

Figure 1. Chemical structure of Almotriptan malate

In literature, several analytical methods such as HPLC[2-3], HPTLC[4], HPLC-MS/MS[5], LC-ESI-MS/MS[6], UV Spectrometric [7-8] and Fluorometric and Coloricmetric[9] have been reported for the determination of AM in biological fluids (considerable more) and formulations (less).

Even though there is one visible spectrophotometric method using TCNQ reported for the determination of the drug they are tedious and less specificity. The functional groups present in the drug not fully exploited. Nevertheless, there still exists a need for development of sensitive accurate and flexible visible spectrophotometric methods for the determination of AM in pharmaceutical preparations.

The authors have made some attempts in this direction and succeeded in developing two methods based on the reaction between the drug and Vanillin (method A) or drug and PDAC (method B)[10-11]. These methods can be extended for the routine assay of AM formulations.

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MATERIALS & METHODS (EXPERIMENTAL)

Apparatus and chemicals

A Milton Roy UV/Visible spectrophotometer model-1201 with 10mm matched quartz cells was used for all spectral measurements. All the chemicals used were of analytical grade. AXERT tablets procured from Ortho Mc Nell Pharmaceuticals, USA. Sulphuric acid (14M), Vanillin (BDH, 0.4%, w/v 2.63x 10^{-2}M), PDAC (E. Merck, 0.1% w/v 6.31x 10^{-3}M) in methanol was prepared.

Preparation of Standard and sample drug stock solution

About 100mg of AM was dissolved in 100ml of methanol to get 1mg/ml stock solution. It was further diluted with the same solvent to get working standard solution (200µg/ml) for both the methods (A&B).

Sample solution: About 20 tablets were pulverized and the powder equivalent to 100mg of AM was weighed, dispersed in 25ml of IPA, sonicated for 30 minutes and filtered through Whatman filter paper No 41.The filtrate was evaporated and the residue was dissolved in 100 ml of methanol(1mg/ml). It was used as stock sample solution and was further diluted with the same solvent to get working standard solution for methods (A&B).

Determination of wavelength maximum (λ_{max})

Method A: The 2.5 ml of working standard solution of AM (200µg/ml) in methanol was taken in 10ml calibrated tubes and volume of test tube adjusted to 3.0ml with methanol. To this 1.0 ml of Vanillin (2.63x 10^{-2}M) and 1.0 ml of concentrated sulphuric acid (14M) were added, while cooling under a tap with constant shaking and kept in water bath at 60ºc for 10min. cooled and diluted to the mark with methanol and sonicated for 1 min. to get a concentration of 50µg/ml. In order to investigate the wavelength maximum, the above standard stock solution was scanned in the range of 400-660nm by UV-Visible spectrophotometer. From the spectra (Figure 2), it was concluded that 560nm is the most appropriate wavelength for analyzing AM with suitable sensitivity.

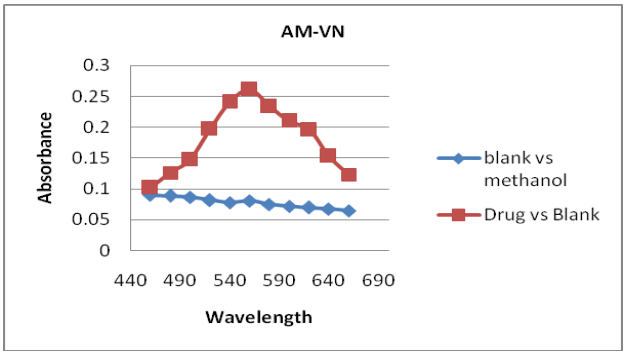

Figure 2. Absorption spectra of AM-VN

Method B: The 3.0 ml of working standard solution of AM (200µg/ml) in methanol was taken in10ml calibrated tubes and volume of test tube adjusted to 3.0ml with methanol. To this 1.0 ml of PDAC(6.31x 10^{-3}M) and 1.0 ml of concentrated sulphuric acid (14M) were added, while cooling under a tap with constant shaking and kept in water bath at 60°C for 10 min. cooled and diluted to the mark with methanol and sonicated for 1 min. to get a concentration of 60µg/ml. In order to investigate the wavelength maximum, the above standard stock solution was scanned in the range of 400-660nm by UV-Visible spectrophotometer. From the spectra (Figure3), it was concluded that 565nm is the most appropriate wavelength for analyzing AM with suitable sensitivity.

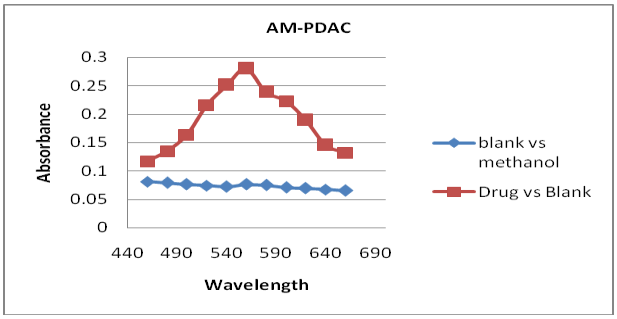

Figure 3. Absorption spectra of AM-PDAC

Preparation of calibration curve:

Method A: Aliquots of standard drug solution in methanol (0.5-2.5ml, 200µg/ml) were placed in a series of 10ml calibrated tubes and volume of each test tube adjusted to 3.0ml with methanol. To each of these test tubes 1.0 ml of Vanillin (2.63x 10^{-2}M) and 1.0 ml of concentrated sulphuric acid (14M) were added, while cooling under a tap with constant shaking and kept in water bath at 60°C for 10 min. cooled and diluted to the mark with methanol. The absorbance was measured at 560nm against the reagent blank within 10 minutes. The amount of drug in a sample was computed from Beer's law plot (Figure4).

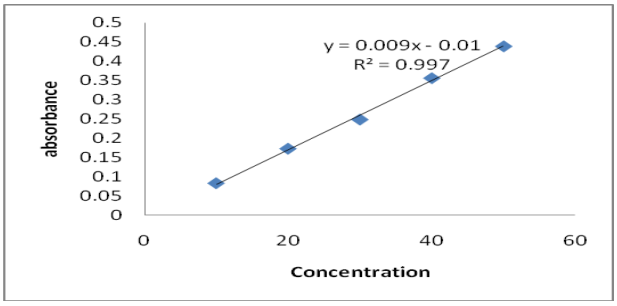

Figure 4. Beer's Law plot of AM-VN

Method B : Aliquots of standard drug solution in methanol (1.0ml-3.0ml, 200µg/ml) were placed in a series of 10ml calibrated tubes and volume of each test tube adjusted to 3.0ml with methanol. To each of these test tubes 1.0 ml of PDAC(6.31x 10^{-3}M) and 1.0 ml of concentrated sulphuric acid (14M) were added, while cooling under a tap with constant shaking and kept in water bath at 60ºc for 10min. cooled and diluted to the mark with methanol. The absorbance was measured at 560nm against the reagent blank within 10 minutes. The amount of drug in a sample was computed from Beer's law plot (Figure5).

RESULTS AND DISCUSSIONS

The optical characteristics such as Beer's law limits, Sandell's sensitivity, molar extinction coefficient, percent relative standard deviation (calculated from the eight measurements containing 3/4th of the amount of the upper Beer's law limits)were calculated for all the methods 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),% range of error (0.05 and 0.01 confidence limits) were calculated for both the methods and are shown in Table-1.

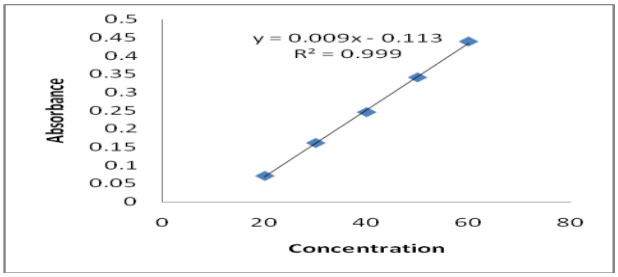

Figure 5. Beer's Law plot of AM-PDAC

Table 1. Optical characteristics, precision and accuracy of the proposed methods

Parameters	Method A	Method B
λ_{max}(nm)	560	565
Beer's law limit (µg/ml)	10- 50	20-60
Sandell's sensitivity (µg/cm²/0.001 abs. unit)	0.012096774	0.016260163
Molar absorptivity (Litre/mole/cm)	38816.96	28877.94
Regression equation (Y) *= a +b x		
Intercept (a)	-0.01	-0.113
Slope(b)	0.009	0.009
%RSD	1.364	1.859
% Range of errors(95% Confidence limits)		
0.05 significance level	1.43	1.951
0.01 significance level	2.24	3.06

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

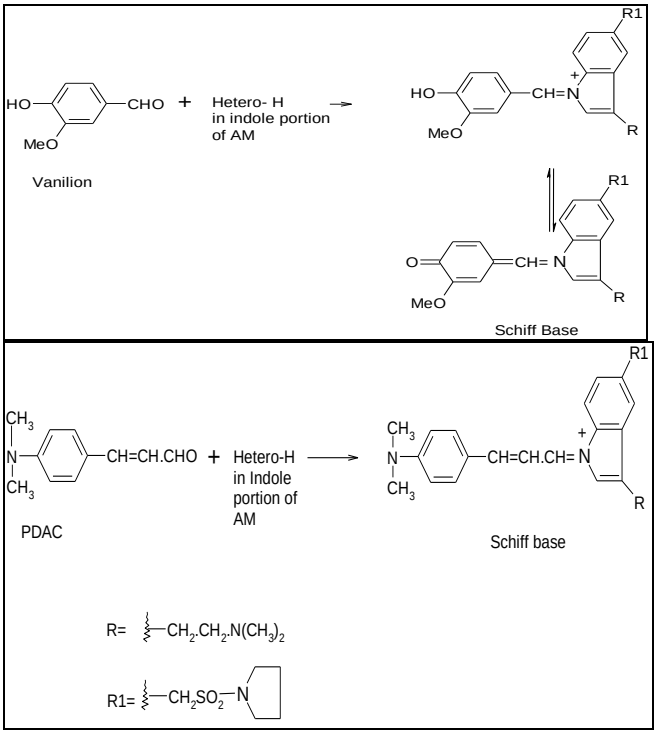

Figure 6. Scheme of reactions

Table 2. Analysis of AM in pharmaceutical formulations

Method	*Formulations	Labeled Amount (mg)	Found by Proposed Methods			Found by Reference Method ± SD	#% Recovery by Proposed Method ± SD
			**Amount found ± SD	t	F		
A	Tablet-1	6.25	6.207±0.029	0.283	1.402	6.21±0.034	99.31±0.46
	Tablet-2	12.5	12.39±0.071	0.675	4.49	12.44±0.15	99.11±0.57
B	Tablet-1	6.25	6.20±0.0346	0.744	1.05	6.21±0.034	99.23 ± 0.554
	Tablet-2	12.5	12.42 ± 0.116	0.34	1.69	12.44±0.15	99.37 ± 0.93

*Tablet- 1 and Tablet-2: 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).

Commercial formulations containing AM were successfully analyzed by the proposed methods. 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 of the drug to the pre-analyzed formulations at three different concentration levels (80%, 100% and 120%). These results are summarized in Table-2. The ingredients usually present in formulations of AM did not interfere with the proposed analytical methods. Among the four aromatic aldehydes (vanillin, PDAC, PDAB and anisaldehydes) tried, all of them responded. But, Vanillin and PDAC were preferred as they were found to be better sensitivity in the assay of AM. MS Excel Software-2007 used for calculations and graphs. The proposed methods are found to be simple, sensitive and accurate and can be used for the routine quality control analysis of AM in bulk and dosage forms.

Chemistry of colored species: In proposing the nature of colored species formation with vanilion(method-A) or PDAC to form schiff base as AM behave like aromatic seconadary amine due to presence of cyclic imino group in indole portion. The formation of colored species with these reagents may be assigned through above analogy as shown in Figure6.

CONCLUSION

The proposed visible spectrophotometric methods for the assay of AM are possess reasonable precision, accuracy, simple, sensitive, and can be used as alternative methods to the reported ones for the routine determination of AM depending on the need and situation.

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