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Spectrophotometric Determination of Almotriptan Malate in Tablets Using Ammonium Molybdate and Phosphomolybdic Acid as Reagents

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Abstract

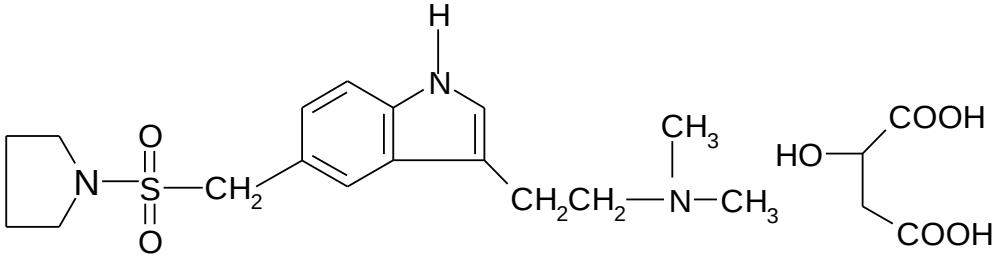
Two simple, sensitive visible spectrophotometric methods have been developed for the estimation of almotriptan malate either in pure or tablet dosage forms. These methods are based on the precipitate /color formation by the reaction of drug with either reagents PMA-Co(II)-EDTA at 840nm (Method A) or ammonium molybdate-potassium thiocyanate in acid medium at 465nm (Method B). Beer's law obeyed in the concentration range of 16-48 µg/ml and 4-20 µg/ml for method A and method B respectively. 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 methods.

Keywords: Assay; Beer's Law; Precipitate/color formation; Statistical analysis; Tablets.

1. 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 [1], visible spectrophotometric [11-15] 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. Molybdenum forms compounds corresponding to the oxidation states +2 and +6. Phosphomolybdic aci ($H_3PO_4.12MoO_3.2H_2O$) is widely employed as a reagent in the quantitative analysis of several drugs. It forms insoluble complexes (yellow precipitate) with various groups of drugs like alkaloids, transquilizers, anti histamines etc., which are usually measured by gravimetry or colorometry due to blue-green color formation by the reduction of phosphomolybdic acid. The reduction of phosphomolybdic acid by various reducing agents like ascorbic acid, hydrazine hydrate to yield molybdenum blue is well known. But the reduction of phosphomolybdic acid by Co(II)-EDTA complex has not been exploited. So the authors have made some attempts in this direction and succeeded in developing method A.

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Molybdate forms insoluble complexes (white precipitate) with various organic compounds of basic nature (amines and heterocyclic compounds) [16] estimated two drugs (Amidoquine and Chloroquine) by precipitating them with ammonium molybdate and estimating the released molybdate (from the precipitate with acetone) with potassium thiocynate in acid medium gives orange yellow colored product owing to the formation of $Mo(NCS)_6^{3-}$ [17] under specified experimental conditions. Based on it, Method B is developed. These methods are extended for the routine assay of AM drug formulations.

2. Materials & Methods (Experimental)

2.1. 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.

2.1.1. Method A

PMA solution (Rea chem, 4%, $2.194x10^{-2}$M): Prepared by dissolving 4g of phosphomolybdic acid in100ml distilled water, Cobalt nitrate solution(BDH, 3%, $1.03x10^{-1}$M): prepared by dissolving 3g of cobalt nitrate in 100ml of distilled water, EDTA solution (Sd-fine,4%, $1.07x10^{-1}$M): prepared by dissolving 4g of disodium salt of ethylene diamine tetra acetic acid in 100 ml of distilled water and AR grade acetone reagents were used

2.1.2. Method B

Ammonium molybdate (AM) solution (E-Merck, 2%, $1.618x10^{-2}$M) :Prepared by dissolving 2 g of ammonium molybdate in 100 ml of distilled water, PTC solution (Ranbaxy, 10%, 1.029M): Prepared by dissolving 10 g of potassium thiocyanate in 100 ml of distilled water and HCl concentrated (E-Merck) were used .

2.2. Preparation of Standard Drug Stock Solution

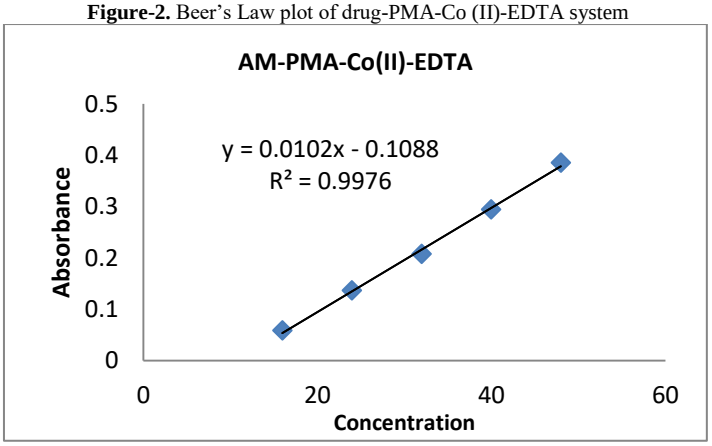
An accurately weighed quantity of 100 mg pure AM drug was dissolved in little amount of water and made to 100ml with distilled water. The prepared stock solution was stored at 4^0 C protected from light. This stock standard solution was further diluted stepwise with distilled water to obtain working standard solution (400µg/ml for method A, 200µg/ml for method B) and a series of standards were freshly prepared during the analysis day.

2.3. Analysis of Bulk Samples

2.3.1. Recommended Procedure for Method A

Aliquots of the standard AM solution ((1.0-3.0ml, 400µg/ml) were delivered into a series of centrifuge tubes and the volume in each tube was adjusted to 3.0ml with distilled water. 2.0 ml ($2.194x10^{-2}$M) of phosphomolybdic acid was added and centrifuged for 5 minutes. The precipitate was collected through filtration followed by washing with distilled water until it is free from the reagent. The precipitate in each tube was dissolved in 5 ml of acetone and transferred into a 25 ml graduated tube. 1.0 ml ($1.03x10^{-1}$M) of cobalt nitrate and 1.0 ml ($1.07x10^{-1}$M) of EDTA solutions were successively added and the tubes were heated for 12 min at 60°C. The tubes were cooled and the solution in each tube was made up to the mark with distilled water. The absorbance was measured at 840nm against a similar reagent blank omitting the drug. The amount of drug in a sample was calculated from Beer's law plot (Figure 2).

Figure-2. Beer's Law plot of drug-PMA-Co (II)-EDTA system

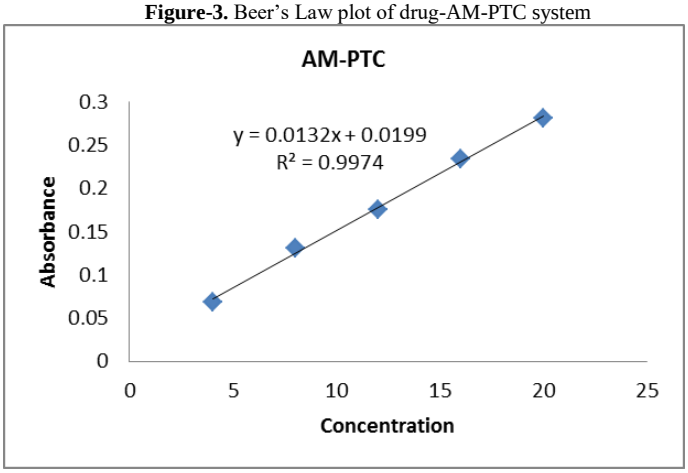


2.3.2. Recommended Procedure for Method B

Aliquots of standard AM drug solution (0.5-2.5ml, 200µg/ml) were delivered into a series of centrifuge tubes and the volume in each tube was adjusted to 3.0 ml with distilled water. 1.0ml ($1.618x10^{-2}$M) of ammonium molybdate was added and centrifuged for 5 min. The precipitate was collected through filteration followed by washing with 50% alcohol until it is free from the reagent. The precipitate in each tube was dissolved in 5 ml of acetone and transferred into a 25 ml graduated tube. Then 5 ml of conc. HCl and 3.0 ml (1.029M) of potassium

thiocyanate were successively added. The tubes were kept aside for 20 min at laboratory temperature. The solution in each tube was made up to the mark with distilled water. The absorbance was measured at 465nm against a similar reagent. The amount of drug in a sample was calculated from Beer's law plot (Figure 3).

Figure-3. Beer's Law plot of drug-AM-PTC system



2.4. Analysis of Tablets

About 20 tablets were weighed to get average tablet weight and pulverized. The powder equivalent to 100mg of AM drug was weighed and extracted with $CHCl_3$ (2x15ml), and filtered through whatman filter paper no.41. The filtrate was evaporated and the residue was used for the preparation of working sample solutions in the same way as under working standard solution.

3. Results and Discussion

The optimum conditions for the development of the methods were 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. The volume of addition of reagents, order of addition of reagents, time required for maximum color development, solvent for final dilution and stability period of the colored species were studies. Among different solvents, acetone is preferred for dissolving precipitate and release phosphomolybdeic acid and molybdate in method A &B respectively. 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. Regression characteristics like standard deviation of slope (S_b), standard deviation of intercept (S_a), standard error of estimation (S_e) and % range of error (0.05 and 0.01 confidence limits) were calculated and their results 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 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.

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

Parameters	**Method A**	**Method B**
λ_{max}(nm)	840	465
Beer's law limit(µg/ml)	16-48	4-20
Sandell's sensitivity(µg/cm^2/0.001 abs. unit	0.006183575	0.002742857
Molar absorptivity (Litre/mole/cm)	75936.65625	171193.75
Regression equation *Y= a +b x		
Intercept (a)	-0.108	0.019
Slope(b)	0.01	0.013
%RSD	2.02	0.956
% Range of errors(95% Confidence limits)		
0.05 significance level	2.12	1.002
0.01 significance level	3.33	1.57
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*Y = a+ b x, where Y is the absorbance and x is the concentration of AM in µg/ml
**calculated from six determinations

Table-2. Analysis of Almotriptan Malate in Tablets

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	6.19 ±0.046	2.66	1.83	6.21±0.034	99.01±0.73
B	Tablet-1	6.25	6.16±0.082	1.52	5.81	6.21±0.034	98.61 ±1.31

* 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).

3.1. Chemistry of Colored Species

The Method A concerns with the quantitative precipitation of AM drug with Phospho molybdeic acid (first step) and estimating the PMA released (with acetone from its adduct), by reducing it with Co(II)-EDTA complex (second step). The probable sequences of reactions in two steps based on analogy are presented in Figure 4.

The Method B involves the quantitative precipitation of AM drug with ammonium molybdate (first step) and estimating the molybdate released (with acetone from its adduct) by complexing it with potassium thiocyanate (second step) The probable sequences of reactions in two steps based on analogy are presented in Figure 5.

Figure-4. Probable Sequence Reactions Of The Proposed Method A

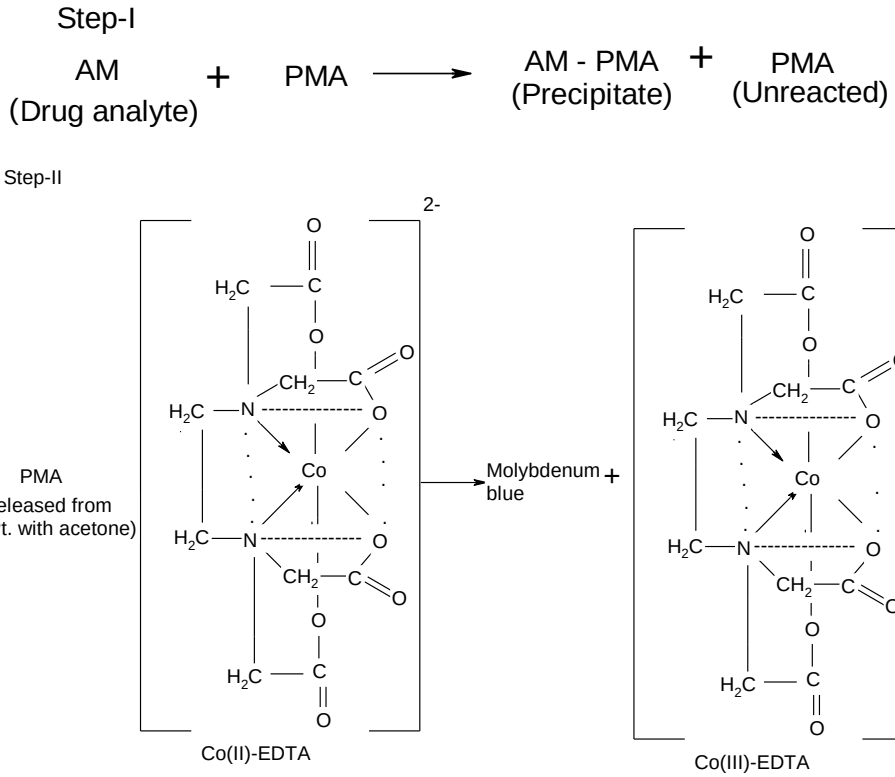
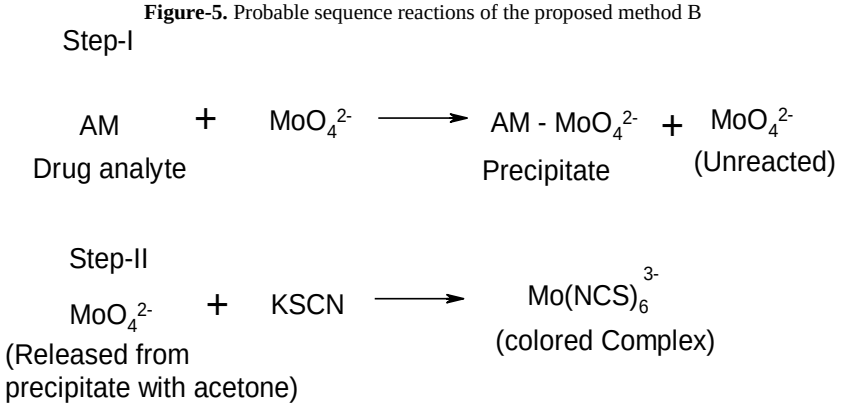


Figure-5. Probable sequence reactions of the proposed method B



4. Conclusion

The reagents utilized in the proposed methods are normal cost, readily available and the procedure does not involve any critical reaction conditions or tedious sample preparation. The proposed methods possesses reasonable precision, accuracy and is 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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