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Spectrophotometric Methods for the Estimation of Pramipexole Dihydrochloride in Pharmaceutical Formulations

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Abstract: Two simple, sensitive, accurate and economic methods A and B have been developed for the quantitative estimation of pramipexole dihydrochloride drug and its formulations (Tablets). Method A is based on the diazotization of primary amine group of pramipexole with sodium nitrate and hydrochloric acid followed by coupling with N-(1-napthyl) ethylene diamine hydrochloride (BM Reagent) to form a colored chromogen with a characteristic absorption maximum at 616 nm.. Method B is based on the reaction of the drug in methanolic solution with paradimethylaminobenzaldehyde (PDAB) in acidic condition producing Schiff's base having a λ_{max} at 474.5nm. Beer's law is obeyed in concentrations ranging from 4-20 µg/ml for method A and 50-150 µg/ml for method B. The results obtained with the proposed methods are in good agreement with labeled amounts when the marketed pharmaceutical formulations are analyzed. The results of analysis have been validated statistically and by recovery studies.

Key words: Pramipexole dihydrochloride · Paradimethylaminobenzaldehyde (PDAB) · Spectrophotometric · N-(1-napthyl) ethylene diamine hydrochloride

INTRODUCTION

Pramipexole dihydrochloride is chemically (s)-2-amino-4,5,6,7-tetrahydro-6-(propylamino) benzothiazole dihydrochloride (Fig. 1) which is a non-ergot dopamine agonist recently approved for the treatment of early and advanced Parkinson's disease (PD). It is used along with levodopa. It is also used in restless legs syndrome. Pramipexole is licensed in the United Kingdom for the treatment of advanced Parkinson's disease in conjunction with levodopa therapy.

Very few analytical methods have been developed for its quantitative estimation in pharmaceutical formulations, which include analysis of biological fluids using LC-MS[2-4], electrophoresis[6] with laser-induced fluorescence detection methods. In view of the above fact, some alternative, simple and economical methods are required for its quantitative estimation of Pramipexole dihydrochloride.

Two simple, sensitive and economic methods (A and B) have been developed by using BM Reagent and paradimethylaminobenzaldehyde (PDAB).

Method A is based on the diazotization of the free amino group in Pramipexole dihydrochloride with sodium nitrite and hydrochloric acid followed by coupling with N-(1-napthyl) ethylene diamine hydrochloride (BM Reagent) which is detected at 616 nm. Beer's ranges from 4-20 µg/ml. Method B is based on the reaction of the free amino group[7] in pramipexole dihydrochloride in methanolic solution with paradimethylaminobenzaldehyde (PDAB) in acidic condition along with the supply of heat, producing Schiff's base having a λ_{max} at 474.5 nm. Beer's law is obeyed in concentrations ranging from 50-150 µg/ml. Spectrophotometric parameters are established for the standardization of the methods including statistical analysis of the data. These methods have been successfully extended to the pharmaceutical dosage forms (tablets) containing free amino group. The probable reaction mechanism given in the Scheme 1.

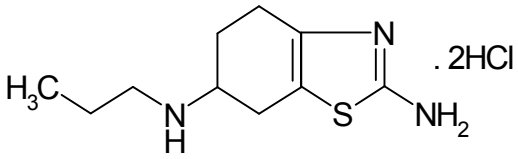

Fig. 1: Pramipexole dihydrochloride

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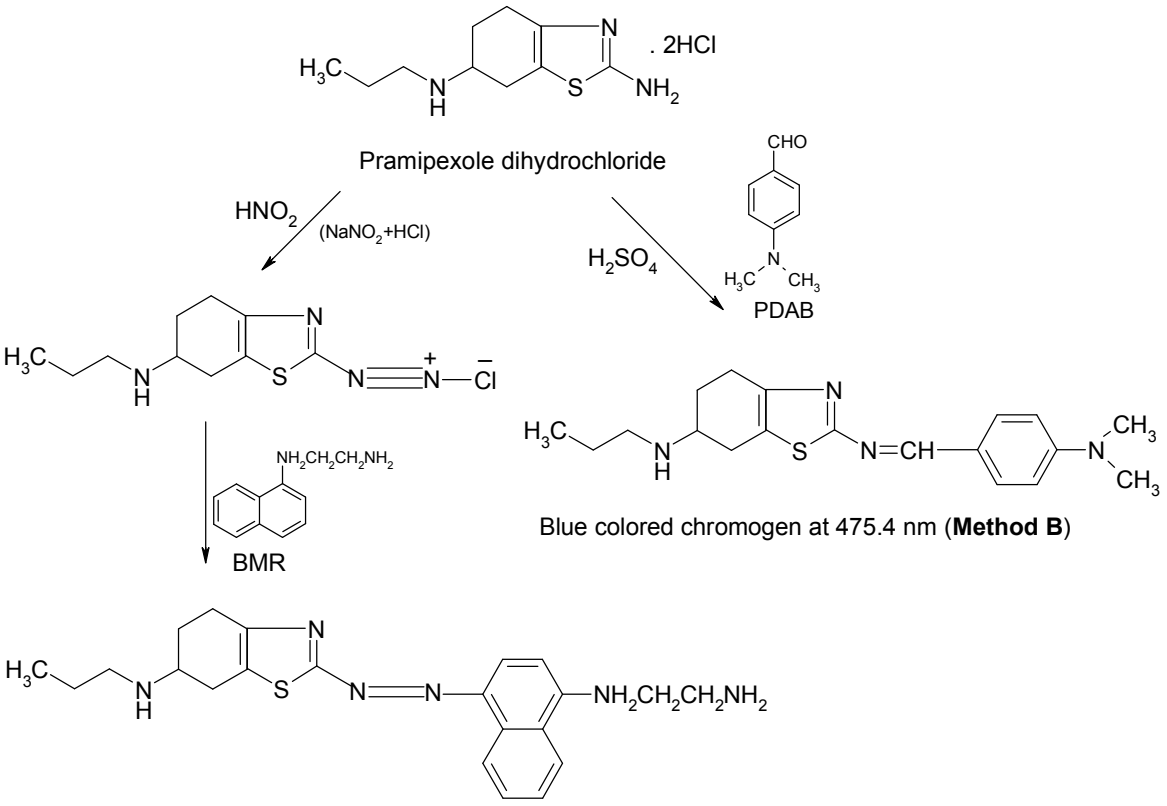

Scheme 1:

Scheme 1

Experimental

Instruments: A Shimadzu model 1700 double beam UV/Visible spectrophotometer with 1cm matched quartz cells was used to measure the absorbance of the resulting solutions.

Reagents: All chemicals and reagent used were of analytical grade and obtained from s. d. fine- chem.,

Mumbai, India. Bulk drug of pramipexole dihydrochloride was obtained from Sun Pharmaceutical Industries, Kartholi, Baribrahmana-Jammu, India. The reagents like 0.1 N sodium nitrite, 0.1 N ammonium sulfamate and 0.1 % N-(1-napthyl) ethylene diamine dihydrochloride (BM reagent) were prepared in distilled water. 0.5 % w/v of PDAB in methanol was prepared.

Preparation of standard drug solution: 100 mg of the bulk drug was weighed accurately, dissolved in 25 ml of methanol in a 100ml volumetric flask and the solution was made up to 100 ml with methanol. From the above stock solution, 10ml of solution was pipetted out carefully into a 100ml volumetric flask and the solution was made up to 100 ml with methanol (100 µg/ml).

Preparation of sample drug solution: For the sample solution, tablets of pramipexole dihydrochloride were accurately weighed and average weight per tablet was determined. The tablets were powdered and powder equivalent to 100 mg of drug was taken into 100 ml volumetric flask and dissolved in 25 ml methanol and shaken for 15 min. and made up to 100 ml with methanol and filtered. This solution was brought to 100 µg/ml with methanol.

Assay Procedure for Pharmaceutical Tablets

Method A: For method B Aliquots of drug ranging from 0.4 -2 ml (1ml=1000 µg/ml) were transferred in a series of10ml volumetric flask. To each of the flask 0.5 ml of 0.1N hydrochloric acid and 0.5 ml of 0.1N sodium nitrite were added mixed and kept aside for 3 mins, then 0.5 ml of 0.1 N ammonium sulfamate was added and the volumetric flask were kept at room temperature for 3 min for complete

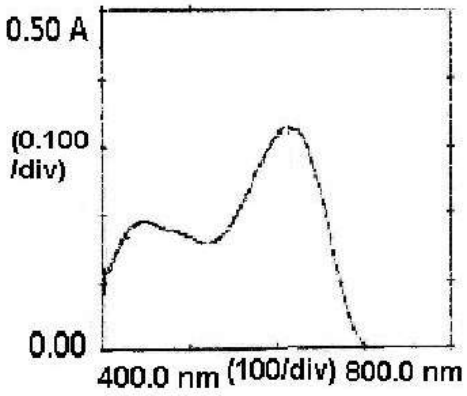

Fig. 2: Absorption spectrum of Pramipexole dihydrochloride with BM reagent at λ_{max} 616 nm (Method A)

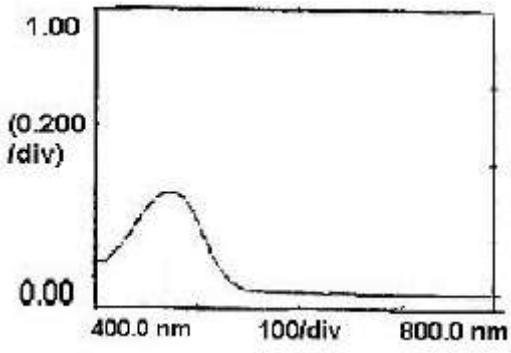

Fig. 3: Absorption spectrum of Pramipexole dihydrochloride with PDAB at λ_{max} 474 (Method B)

neutralization of excess nitrous acid formed in the reaction. Then finally 0.5 ml of BM reagent solution was added and mixed well. The volumes were made up to 10 ml with distilled water. The absorbance of the yellow colored chromogen was measured at 616 nm against reagent blank. The amount of pramipexole dihydrochloride present in the sample was computed from calibration curve (Fig 2).

Method B: Aliquots of drug ranging from 0.5-1.5ml (1ml=1000 µg/ml) were transferred in a series of 10ml volumetric flask. To each of the flask 2.0ml of methanolic PDAB and 1.5ml of 0.1N H_2SO_4 and were added and warmed on a water bath for 2 min and kept aside for 15 min. at room temperature, the color development was developed. The volume was made up to mark with methanol. The absorbance of the yellow colored chromogen was measured at 474.5nm against reagent blank. The amount of Pramipexole dihydrochloride present in the sample was computed from calibration curve (Fig 3).

RESULTS AND DISCUSSION

The optical characteristics such as absorption maxima, Beer´s law limits, molar absorptivity and Sandell´s sensitivity are presented in Table 1. The regression analysis using method of least squares was made for the slope (b), intercept (a) and correlation (r) obtained from different concentrations and results are summarized. The percent relative standard deviation and range of error (0.05 and 0.01 level of confidence limits) calculated from the eight measurements, ¾ of the upper beer´s law limits of pramipexole dihydrochloride.

Table 1: Optical characteristics and precision of the proposed method

Characteristics	Method A	Method B
$\lambda_{max\ (nm)}$	616nm	474.5
Beer's law limits (μg/ml)	5-25	50-150
Molar absorptivity(L/mol/cm)	7.61×10^3	1.063×10^3
Sandell's sensitivity ($\mu g/cm^2$ 0.001 absorbance unit)	0.0373	0.2673
Regression equation (Y*=a+bc)		
Slope(b)	0.030	0.0030
Intercept (a)	0.003	0.0040
Correlation coefficient(r)	0.9970	0.9990
% Relative Standard Deviation (R.S.D)*		
% Range of error (Confidence)**		
0.05 level	0.0010	0.0055
0.01 level	0.0890	0.0080
Limit of Detection (μg / ml)	0.089	0.096
Limit of Quantification (μg /ml)	0.2963	0.3203
Stability (h.)	10	8
Color	yellow	Blue

*Y= bC + a where C is the concentration of pramipexole dihydrochloride in μg/mL and Y is the absorbance at the respective $\lambda_{max.}$

** For eight measurements

Table 2: Results of commercial formulation analysis

Method	Formulation	Labeled amount(mg/tab)	Amount obtained by proposed method	Percentage recovery*	Standard Deviation (±)	Standard Error	% R.S.D
A	PRAMIPEX 0.25	0.25	0.249	99.60	0.586	0.254	0.585
B	PRAMIPEX 0.25	0.25	0.248	99.20	0.354	0.189	0.352

*average of six determination

Table 3: Recovery studies of premipexole dihydrochloride

Method	Labeled amount(mg/tab)	Amount taken (µg mL^{-1})	Amount added		Recovery (% ± S.D)	COV (%)
			%	µg mL^{-1}		
A	PRAMIPEX 0.25	100	80	80	100.46±0.53	0.546
			100	100	101.75±0.35	0.354
			120	120	102.58±0.61	0.625
B	PRAMIPEX 0.25	100	80	80	101.49±0.90	0.751
			100	100	101.19±0.61	0.581
			120	120	100.84±0.79	0.747

The optimum conditions for Method A and the optimum conditions for color development in Method B have been established by varying the parameters one at a time and keeping the other parameters fixed and observing the effects of product on the absorbance and the absorbance of the colored species and incorporated in the procedures. To evaluate the validity and accuracy of the methods, known amounts of pure drug were added to the previously analyzed pharmaceutical preparations and mixtures were analyzed by the proposed methods. The percent recoveries are given in Table 2. Interference studies revealed that the additives like antioxidants, preservatives and solubilises that is usually present in tablets did not interfere at their regularly added levels.

CONCLUSION

The proposed methods are applicable for the assay of drug (Pramipexole dihydrochloride) and have the advantage of wider range under beer´s law limits. The decreasing order of sensitivity and λ_{max} among proposed methods are A>B and B>A, respectively, so the proposed UV and visible spectrophotometric methods are found to be simple sensitive, selective, accurate, precise and economical and can be used in the determination of Pramipexole dihydrochloride in bulk drugs and its pharmaceutical preparations in a routine manner.

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