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Ecofriendly spectrophotometric method development and their validation for quantitative estimation of Pramipexole Dihydrochloride using mixed hydrotropic agent

Nilesh Jain*¹, Ruchi Jain¹, Sneha Kulkarni¹, Deepak Kumar Jain² and Surendra Jain¹

¹Sagar Institute of Research and Technology-Pharmacy, Bypass Road, Bhopal
²Truba Institute of Pharmacy, Karond Gandhi Nagar Bypass Road Bhopal, India

ABSTRACT

A novel, safe, accurate, sensitive and economic Spectrophotometric method was developed by application of mixed hydrotropy using 2 M sodium acetate and 8 M urea solution (50:50% V/V) as hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble pramipexole dihydrochloride (solubility:- 1.4×10^{-01} mg/ml in water) in tablet dosage form. The solubility of Pramipexole Dihydrochloride increases more than 46 times in mixed hydrotropic solution as compared to solubility in distilled water. Pramipexole dihydrochloride shows maximum absorbance at 262 nm. Sodium acetate, urea and other tablets excipients did not show any absorbance above 250 nm and thus no interference in the estimation was seen. Pramipexole dihydrochloride was obeyed Lambert Beer's law in the concentration range of 15 to 75 $\mu\text{g/ml}$ ($r^2 = 0.9997$) in mixed hydrotropic agent with mean recovery was found $98.35 \pm 0.55\%$. The percent concentration in marketed tablet formulation was found $97.52 \pm 1.65\%$. Parameters such as linearity, precision, accuracy, specificity and robustness were studied as reported in the International Conference on Harmonization guidelines. The relative standard deviations for three replicate measurements in five concentrations of samples were always less than 2%. So this method can successfully employ in the routine analysis of pramipexole dihydrochloride in bulk drug and tablet dosage forms.

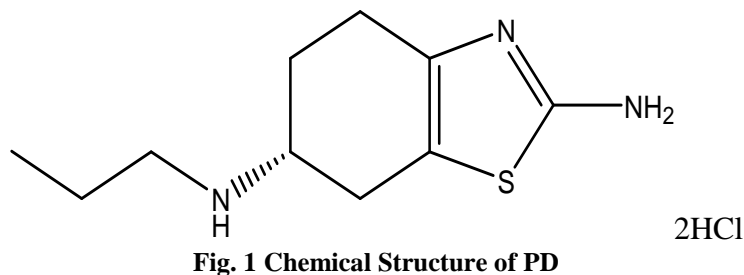
Keywords: Pramipexole Dihydrochloride, mixed hydrotropic solution (sodium acetate & urea), spectrophotometry.

INTRODUCTION

Pramipexole Dihydrochloride (PD) [1], is chemically (s)-2-amino-4, 5, 6, 7-tetrahydro-6-(propylamino) benzothiazole dihydrochloride. It is recently approved for the treatment of early and advanced parkinson's disease. Hydrotropy phenomenon is considered as unique technique by

which solubility of sparingly soluble solute under normal conditions increases several folds. Nilesh *et al*, Maheshwari *et al* have been employed various techniques to enhance the aqueous solubility [2-15]. Sodium salicylate, sodium benzoate, urea, niacinamide, sodium citrate and sodium acetate are the most common examples of hydrotropic agents utilized to increase the water solubility. Various organic solvents such as methanol, chloroform, dimethyl formamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out spectrophotometric analysis. Drawbacks of organic solvents include their higher cost, toxicity and pollution. Hydrotropic solution may be a proper choice to preclude the use of organic solvents.

Very few analytical methods have been developed for its quantitative estimation in pharmaceutical formulations by UV [16], biological fluids using LC-MS [17-19], capillary electrophoresis with laser-induced fluorescence detection methods [20]. In view of the above fact, some alternative, simple and economical methods required for its quantitative estimation of pramipexole dihydrochloride. In the preliminary solubility studies there were more than 46 fold enhancements in the solubility of PD in mixed hydrotropic solution. Therefore, it was thought worthwhile to employ this hydrotropic solution to extract out the drug from fine powder of tablets to carry out spectrophotometric estimation. The chemical structure of PD is shown in Fig. 1



EXPERIMENTAL SECTION

Apparatus

The proposed work was carried out on a Shimadzu UV-visible spectrophotometer (Model UV-1700 series), which possesses a double beam, double detector configuration with matched 1 cm quartz cells.

Reagents and Standards

Reference standard of PD was a generous gift from Sun Pharmaceuticals Ind. Ltd., Mumbai, sodium acetate and urea obtained from Merck Chemical Division, Mumbai. Commercial tablets of PD, Pramipex (Sun Pharmaceuticals Ind. Ltd.) was procured from the local drug market. Label claim of PD in tablet is 0.5 mg.

Preliminary Solubility Studies

Solubility of PD was determined in distilled water and mixed hydrotropic solution of 8 M urea and 2 M sodium acetate solution (50:50% V/V) at $25 \pm 1^\circ$. There was more than 46 folds solubility enhancement in mixed hydrotropic solution, as compare to distilled water. The enhancement of solubility is due to the hydrotropic solubilization phenomenon.

Preparation of calibration curve

Accurately weighed 100 mg of the PD drug sample were transferred in to 100 ml volumetric flask and it solubilized by 100 ml of mixed hydrotropic solution, containing 8 M urea and 2 M sodium acetate solution (50:50% V/V).The standard solution (1000 μ g/ml) was further diluted

with distilled water to obtain 15, 30, 45, 60 and 75 $\mu\text{g}/\text{ml}$. Detection wavelength was selected for PD was 262 nm. Absorbances were noted against distilled water as blank. Calibration curve was plotted between concentration verses absorbance. Spectra of PD were shown in Fig. 2

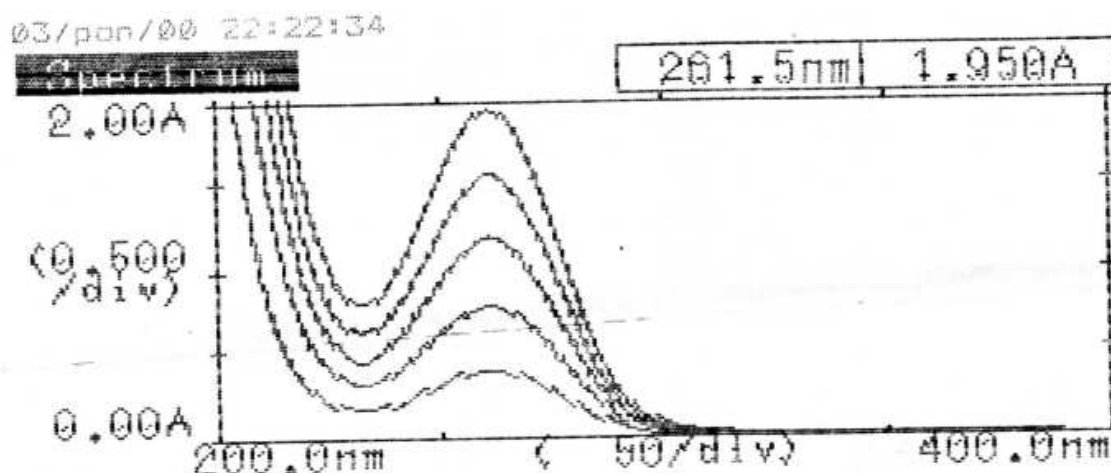


Fig. 2 UV Spectra of PD

Analysis of Tablet Formulation

Marketed formulation Pramipex (Sun Pharmaceuticals Ind. Ltd.) was selected for tablet analysis. Twenty tablets of PD were weighed and ground to a fine powder. An accurately weighed powder sample equivalent to 10 mg of PD was transferred to 10 ml of volumetric flask containing 8ml of mixed hydrotropic solution, comprised of 8 M urea and 2 M sodium acetate solution (50:50% V/V). Then the volume was made up to 10 ml by addition of an above solution. The flask was sonicated for about 30 min to solublize the drug. The solution was filtered through Whatmann filter paper No. 41. The filtrate was diluted appropriately with distilled water and was analyzed on UV spectrophotometer against distilled water as blank. Drug content of tablet formulation were calculated using calibration curve and value are reported in Table-1 and Table-2.

Recovery studies

To evaluate the recovery studies, to pre-analyzed tablet solution, a definite amount of drug was added. These studies were performed by taking different conc. ranging from 15-75 $\mu\text{g}/\text{ml}$ and analyze them. Bulk drug samples ranging from 15-75 $\mu\text{g}/\text{ml}$ were added as spiked concentrations and drug contents were determined by the proposed analytical method. Result of recovery studies were presented in Table-3.

Precision studies

To evaluate precision at different parameter like repeatability, intermediate precision, five dilutions in three replicates were analyzed in same day, in two different days by two analysts for day to day and analyst to analyst variation. Results were shown in Table-4.

Robustness

As per ICH norms, small but deliberate variations by altering the pH and / or concentration of the solvent were made to check the methods capacity to remain unaccepted. The change was made in the combination of mixed hydrotropic solution, containing 8 M urea and 2 M sodium acetate solution (50:50% V/V). Instead of 50:50 ratio, 60:40 ratio of sodium acetate and urea was used as solvent.

RESULT AND DISCUSSION

Based on the solubility and stability and spectral characteristics of the drug, mixed hydrotropic solution, containing 2 M sodium acetate and 8 M urea solution (50:50% v/v) was selected as hydrotropic agent. PD solublized in the selected hydrotropic agent was scanned in spectrum mode and 262 nm was selected as wavelength for estimation of the drug. The developed method was found to be linear in the range of 15-75 $\mu\text{g/ml}$ with correlation coefficient (r^2) of 0.999. The mean Percent label claims of tablets of PD in estimated by the proposed method was found to be $97.52 \pm 1.65\%$. These values are close to 100, indicating the accuracy of the proposed analytical method. Low values of standard deviation, percent coefficient of variation and standard error further validated the proposed method Table-1 and Table-2.

The values of mean percent recoveries were also found ranging from 97.68 to 98.53%. The values of standard deviation, percentage coefficient of variation (0.055) and standard error (0.099) were satisfactorily low Table-3. Results of precision at different level were found be within acceptable limits ($RSD < 2$) Table-4. Presence of hydrotropic agent do not shows any significant interference in the spectrophotometric assay thus further confirming the applicability and reproducibility of the developed method.

Table-1 Result of Tablet Analysis

Amount of drug claimed ($\mu\text{g/ml}$)	Tablet Analysis Using Mixture of 2 M Sodium Acetate, 8 M Urea As Hydrotropic Agent					
	Amount of drug found ($\mu\text{g/ml}$) in tablet			% estimated in formulation		
	Pramipex (0.5 mg)					
	Rep-1	Rep-2	Rep-3	Rep-1	Rep-2	Rep-3
30	28.82	28.91	28.52	96.06	96.36	95.06
45	44.32	44.82	44.7	98.48	99.6	99.33
60	58.44	58.82	58.41	97.4	98.03	97.35

* $n = 9$, (3 conc. in 3 replicates)

Table-2 Statistical Evaluation of Analysis of Tablet

Parameters	Formulation (Pramipex)
Mean % estimated	97.52
Standard deviation	1.65
% Coefficient of variation	1.697
*Standard error	0.30253

* $n = 9$, (3 conc. in 3 replicates)

Table-3 Result of recovery studies of tablet formulation with statistical evaluation

Theoretical conc. ($\mu\text{g/ml}$)	Amount added ($\mu\text{g/ml}$)	% recovery Mean \pm S.D. (n=6)	% Coefficient of variation	*Standard error
15	15	98.73 ± 0.6	0.61	0.25
30	30	97.55 ± 1.0	1.03	0.41
45	45	98.91 ± 0.81	0.83	0.33
60	60	98.48 ± 0.47	0.48	0.20
75	75	98.05 ± 0.21	0.22	0.09

* Mean of Fifteen determinations (3 replicates at 5 concentration level)

Table-4 Result of Precision of PD

Validation Parameters	% Mean \pm S.D* _(n=6)	% RSD
Repeatability	97.68 \pm 0.20	0.53
Intermediate precision		
Day to Day	97.88 \pm 0.38	1.05
Analyst to Analyst	97.54 \pm 0.38	1.17

* Mean of Fifteen determinations (3 replicates at 5 concentration level)

CONCLUSION

It was thus concluded that the proposed method is new, simple, cost effective, accurately, precise, safe and ecofriendly and can be successfully employed in the routine analysis of PD in bulk drug and tablet dosage forms.

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