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Novel Ecofriendly Spectrophotometric Method for Estimation of Ziprasidone Hydrochloride Monohydrate using Hydrotropic Solubilization Technique

R. Jain[1]*, N. Jain[2], S. K. Jain[2]

1.*Suresh Gyan Vihar University, Jaipur, Rajasthan, India-302025*

2.Sagar Institute of Research & Technology-Pharmacy, Ayodhya Bypass Road, Bhopal, Madhya Pradesh, India – 462041

ABSTRACT

A simple, accurate, novel, safe and precise method has been developed for estimation of poorly water soluble drug Ziprasidone Hydrochloride using 2 M Citric acid as hydrotropic agent. After solubilizing the Ziprasidone Hydrochloride in selected hydrotropic agent, it was scanned in spectrum mode and the working wavelength for the estimation, considering the reproducibility and variability was found to be 314 nm. The developed method was found to be linear in the range of 20-100 µg/ml with correlation coefficient (r^2) of 0.9997. The mean percent label claims of tablets of ZIP in formulation-I and formulation-II estimated by the proposed method were found to be 97.92±0.59 and 98.46±0.39 respectively. These values are close to 100, indicating the accuracy of the proposed analytical method. 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. The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values.

Keywords: Ziprasidone Hydrochloride, Citric acid, Hydrotropic solubilizing agents.

*Corresponding Author Email: jainruchi02@gmail.com

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INTRODUCTION

Ziprasidone Hydrochloride (ZIP) is Chemically 5-[2-[4-(1, 2-benzisothiazol-3-yl)-1-piperazinyl]ethyl] -6-chloro-1, 3-dihydro-2H-indol-2-one HCl ((Figure -1). It is the fifth atypical antipsychotic to gain FDA approval (February 2001) for the treatment of schizophrenia[1, 2]. Literature survey for ziprasidone revealed that several analytical methods based on different techniques, viz. LC-MS[3-5]assay, HPLC[6-8] method, LC method[9] with fluorescence and capillary zone electrophoresis[10] method has reported for determination of ziprasidone in pharmaceutical formulations. Hydrotropic solubilization is the phenomenon by which aqueous solubility of poorly water soluble drugs and insoluble drugs increases. Various techniques have been employed to enhance the aqueous solubility and hydrotrophy is one of them. Maheshwari and Jain et al has used sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate are the most common examples of hydrotropic agents utilized to increase the water solubility of drug[11-16]. 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. 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. Present work emphasizes on the quantitative estimation of ZIP in their dosage form by UV Spectroscopic methods.

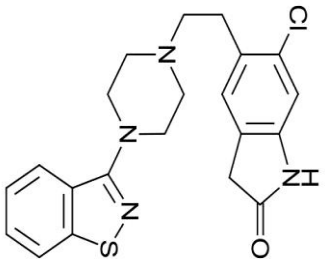

Figure 1: Chemical structure of ZIP

MATERIALS AND METHODS

Instrument

UV-Visible double beam double detector spectrophotometer, Shimadzu model-1700 having spectral bandwidth 3 nm and of wavelength accuracy ±1 nm, with 1cm quartz cells was used.

Reagents and chemicals

Analytical pure sample of ZP was supplied as gift sample from Torrent Pharmaceuticals Ltd.

Citric acid obtained from Merck Chemical Division, Mumbai. Reverse Osmosis Water was used throughout the study.

Preliminary solubility studies of drugs

A definite amount of drug was added to a screw capped 25 ml of volumetric flask containing different aqueous systems viz distilled water, different hydrotropic agent and 2M Citric acid. The volumetric flasks were shaken mechanically for 12 hrs at 25±1°C in a mechanical shaker. These solutions were allowed to equilibrate for next 24 hrs and then centrifuged for 5 min at 2000 rpm. The supernatant liquid was taken for appropriate dilution after filtration through whatman filter paper no. 41 and analyzed spectrophotometrically against R.O. water as blank. After analysis, it was found that the enhancement in the solubility of ZIP was to be more than 56 folds in 2M citric acid solution as compared to solubility studies in other solvents[17].

Selection of hydrotropic agent

ZIP was scanned in hydrotropic agent in the spectrum mode over the UV range (200-400) and 2 M citric acid as hydrotropic agent were found to be most appropriate because:

- ZIP is soluble in it (56 fold enhancement of solubility)
- ZIP is stable in hydrotropic agent (as per the stability profile)
- ZIP exhibit good spectral characteristics in it.
- Citric acid solution has no interference with the λ_{max} of ZIP 314 nm (Figure 2).

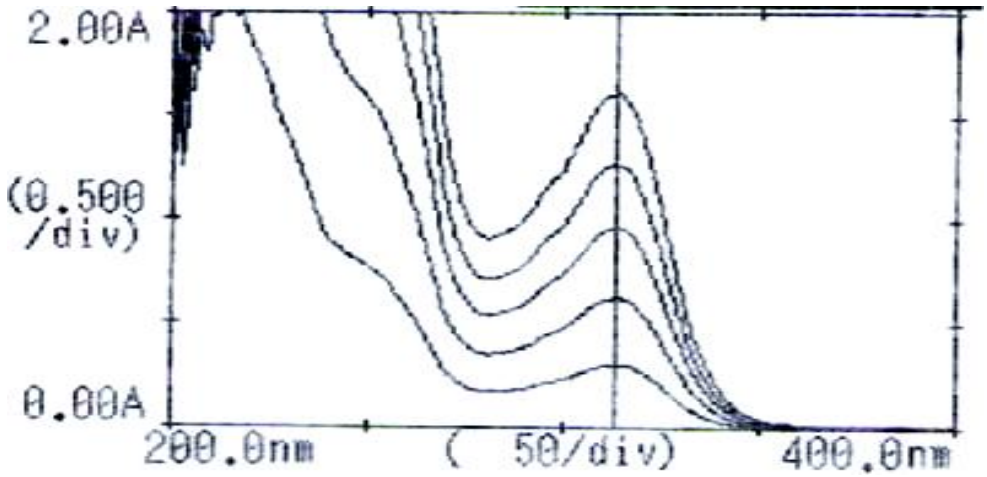

Figure 2: Spectra of ZIP in 2 M Citric Acid as Hydrotropic Agent

Establishment of stability profile:

Stability of ZIP was observed by dissolving in 2 M citric acid as hydrotropic agent. Solution of ZIP was prepared in the conc. of 60 µg/ml and scanned under time scan for 30 min. Spectra of drug under time scan shows that drug are stable in hydrotropic solution.

Linearity range and calibration graph:

Preparation of Standard Stock Solution (Stock-A)

Accurately weighed 100 mg of the ZIP was transferred in to 100 ml volumetric flask containing 80 ml of 2 M citric acid as hydrotropic agent and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to the mark with hydrotropic agent to get a concentration of 1000 µg/ml (Stock-A)[17].

Preparation of Working Standard Solution for calibration curve:

Preparation of Working Standard Solution

The standard solution (1000 µg/ml) was further diluted with distilled water to obtain 20, 40, 60, 80 and 100µg /ml solution and absorbance were noted at 314nm against distilled water as blank.

ANALYSIS OF MARKETED FORMULATION

Two marketed formulation Azona capsule (Torrent Pharmaceuticals Ltd.), Zipsydon tablet (Sun Rise International Labs Ltd.) were selected for analysis, i.e. containing 80 mg ZIP. For tablet twenty tablets were accurately weighed, average weight determined and ground to fine powder and for capsule uncapped twenty capsules and average weight determined. Accurately weighed quantity of powder equivalent to 80 mg of ZIP was transferred into 100 ml volumetric flask and dissolve in 80 ml of hydrotropic solution. The flask was sonicated for about 20 min to solublize the drug and filtered through whatman filter paper no. 41. The resulting solution was further diluted. Absorbances of sample solutions were analyzed on UV spectrophotometer at 314nm against R.O. water as blank. Drug content of tablet and capsule formulation were calculated using calibration curve.

VALIDATION PARAMETERS

The developed method was validated as per ICH guidelines (Linearity, Accuracy, Precision and Robustness) [18].

Linearity

Linearity of ZIP was established by response ratios of drug. Response ratio of drug was calculated by dividing the absorbance with respective concentration.

Accuracy

To check the degree of accuracy of the method, recovery studies were performed in triplicate by standard addition method at 80%, 100% and 120%. In preanalyzed tablet solution, a definite amount of drug was added and then its recovery was studied. These studies were performed in by adding fixed amount of pure drug solution to the final dilution while varying the concentration of tablet sample solution in the final dilution[18].

Precision

Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to Day and analyst to analyst) and reproducibility.

Repeatability was performed by analyzing same 5 concentrations of drug for 5 times. Day to Day was performed by analyzing 5 different concentration of the drug for five days in a week[18]. Reproducibility was performed by analyzing same concentration of drugs for five times in different lab[18].

RESULTS AND DISCUSSIONS

Based on the solubility, stability (Table 1) and spectral characteristics of the drug, 2 M Citric acid was selected as hydrotropic agent. There was more than 56 fold solubility enhanced in hydrotropic solution as compare with distilled water. After solubilizing the Ziprasidone Hydrochloride in selected hydrotropic agent, it was scanned in spectrum mode and the working wavelength for the estimation, considering the reproducibility and variability was found to be 314 nm. The developed method was found to be linear in the range of 20-100 µg/ml with correlation coefficient (r2) of 0.9997 and linear equation was Y=0.8085X + 0.0119. Calibration curve was plotted between concentrations versus absorbance; Figure 3. Observation of linearity data has been reported in the Table 2. The Result of their optical characteristics has been reported in Table 3.

Table 1: Stability data of ZIP in 2 M Citric Acid

	2 M Citric Acid as Hydrotropic Agent	
Time.	**Conc.(µg/ml)**	**ABS**
5 min	60	0.984
10 min	60	0.983
15 min	60	0.984
20 min	60	0.984
25 min	60	0.983
30 min	60	0.983

Table 2: Linearity ZIP at λ_{max} =238 nm in 2 M Citric Acid

Standard Conc. (µg/ml)	Rep-1	Rep-2	Rep-3	Rep-4	Rep-5	Mean
0	0	0	0	0	0	0
20	0.306	0.332	0.35	0.348	0.337	0.3346
40	0.628	0.626	0.653	0.638	0.612	0.6314
60	0.969	0.959	0.982	0.98	0.932	0.9644
80	1.274	1.258	1.318	1.346	1.276	1.2944
100	1.518	1.597	1.633	1.629	1.578	1.591
Correlation Coefficient (r^2)						0.9997
Slope (m)						0.8085
Intercept (c)						0.0119

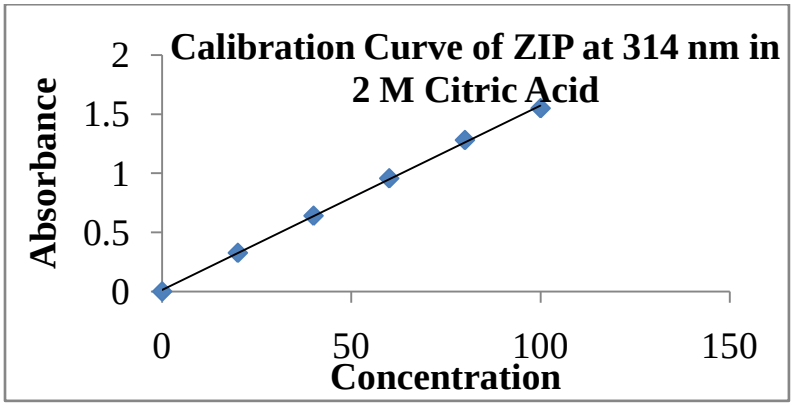

Figure 3: Calibration Curve of ZIP at 314 nm in 2 M Citric Acid

Table 3: Optical Characteristic and Linearity Data of ZIP in 2 M Citric Acid

S.No.	Parameter	2 M Citric Acid
1	Working λ	314 nm
2	Beer's law limit (µg/ml)	20-100
3	Correlation Coefficient (r^2)*	0.9997
4	Slope (m)*	0.8085
5	Intercept (c)*	0.0119
6	Number of samples (n)	25

*Average of 5 determination of 5 concentrations

The mean percent label claims of tablets of ZIP in formulation-I and formulation-II estimated by the proposed method were found to be 97.92±0.59 and 98.46±0.39 respectively. These values are close to 100, indicating the accuracy of the proposed analytical method. The statistical evaluation of tablet analysis has been reported in Table 4. and Table 5.

Table 4: Tablet Analysis Using 2 M Citric Acid

Amount of drug claimed (mg) in tablet	Amount of drug found (mg) in tablet			Percentage estimated in formulation		
	R-I	R-II	R-III	R-I	R-II	R-III
Azona cap-80	79.28	77.32	79.28	99.10	96.65	99.10
Azona cap -80	77.44	77.94	77.98	96.80	97.43	97.48
Azona cap -80	79.17	77.71	78.89	98.96	97.14	98.61
Zipsydon tab-80	78.93	78.67	79.72	98.66	98.34	99.65
Zipsydon tab-80	77.94	78.51	79.04	97.43	98.14	98.80
Zipsydon tab-80	77.93	78.56	79.61	97.41	98.20	99.51

Table 5: Statistical Evaluation of Analysis of Tablet

Parameter	Marketed Tablets	
	Azona Cap-80	**Zipsydon Tab-80**
Mean % estimated	97.92	98.46
Standard deviation %	0.59	0.39
Coefficient of variation	0.607	0.394
*Standard error	0.14029	0.09157

*n=3 in 3 replicates

Linearity was established in the range of 20-100 µg/ml and it was reported as response ratio; Table 6. Then a graph was plotted between concentration and response ratio (Figure 4).

Table 6: Response Ratio of ZIP in 2 M Citric Acid

S. No.	2 M Citric Acid as Hydrotropic Agent		
	Conc.(µg/ml)	ABS	Response Ratio
1.	20	0.312	0.016
2.	40	0.621	0.016
3.	60	0.983	0.016
4.	80	1.23	0.016
5.	100	1.522	0.016

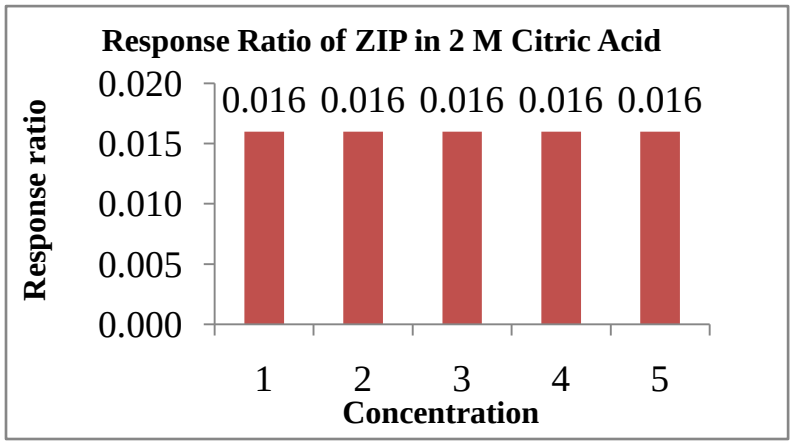

Figure 4: Response Ratio Curve of ZIP in 2 M Citric Acid

The values of mean percent recoveries were also found to show variability in ranging from 97.73±1.01 to 99.82±0.58%. Also the values of standard deviation, percent coefficient of variation and standard error were calculated and reported in Table 7 which is satisfactorily low.

Table 7: Result of Recovery Studies of Tablet Formulation with Statically Evaluation

Drug	QC Conc. (µg/ml)	Recovery Level % (Amount Drug Added)	Amount of Drug Found (Mean±SD)*	% RSD
ZIP	**20**	**80**	97.93±0.84	0.857
		100	98.01±1.03	1.050
		120	99.82±0.58	0.581
ZIP	**40**	**80**	97.73±1.01	1.033
		100	99.04±0.75	0.757
		120	98.45±1.13	1.147

*Average of five determination

Result of precision at different level were found be within acceptable limits (RSD<2), the results has been reported in Table 8. 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 8: Result of Precision of ZIP

	Validation Parameter	Percentage Mean ± S.D*. (n=6)	Percentage RSD
With 2 M Citric Acid	Repeatability	97.45±0.48	1.16
	Intermediate Precision		
	Day to Day	97.02±0.21	0.44
	Analyst to Analyst	96.97±0.28	0.75
	Reproducibility	97.27±0.64	1.42

* Mean of fifteen determinations (3 replicates at 5 concentrations level)

CONCLUSION

Hence, it is concluded that the proposed methods are new, simple, cost effective, accurate, safe and precise and can be successfully employed in the routine analysis of Ziprasidone hydrochloride in bulk drug sample and Tablet Dosage Form. Advantage of these methods is that the organic solvent is not essential for the analysis and there was no interference of 2 M citric acid in the estimation of ZIP. There is a good scope for other poorly water-soluble drugs which may be tried to get solubilized in 2M citric acid solution (as hydrotropic agent) to carry out their spectrophotometric analysis excluding the use of costlier and unsafe organic solvents.

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