Rapid determination of Ziprasidone and Buclizine Hydrochloride in pharmaceutical formulations (Tablets) by simple spectrophotometric method

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ABSTRACT: A simple, sensitive, selective and accurate spectrophotometric method for the determination of Ziprasidone (ZPD) hydrochloride and Buclizine (BUCZ) hydrochloride in bulk drug and pharmaceutical formulations (tablets) has been described. This method is based on the formation of ion-association complex of drug with Alizarin red S (ARS) to form pale pink colored chromogen exhibiting □max 420 nm respectively. The results of analysis for this method have been validated statistically and by recovery studies. The results are compared with those obtained using UV spectrophotometric method in isopropyl alcohol at 229 nm (ZPD), and in Chloroform at 272 nm (BUCZ). The method is simple and sensitive and has been applied successfully to the analysis of laboratory-made tablets without any interference from the tablet excipients.

KEY WORDS: Ziprasidone hydrochloride, Buclizine hydrochloride, spectrophotometric method, Ion – Association complex, statistical analysis, drug recovery studies.

INTRODUCTION

ARS is a dye and a common reagent for the determination of metal ions[1-3] and for some pharmaceutical formulations in spectrophotometric method[4,5]. ZPD is chemically known as 5- [2 - [4- (1, 2 - benzisothiazol-3-yl)-1-piperazin-1yl] ethyl]-6-chloro-1, 3-dihydroindol-2-one hydrochloride. It is a novel antipsychotic with a unique pharmacological profile. It is freely soluble in methanol, ethanol and chloroform, sparingly soluble in acetonitrile and octanol. Ziprasidone exhibits a potent and highly selective antagonistic activity on the D_2 and $5HT_{2A}$ receptors. The metabolic fate of Ziprasidone has been studied in both rats and humans and found to be extensively metabolized in both species [6].

BUCZ is a piperazine antihistamine with antimuscarinic and central sedative properties. Chemically BUCZ is 1-[(4-chlorophenyl) Phenyl methyl] –4-[(4-(1,1 dimethyl ethyl) phenyl] methyl] piperzine; It is mainly used for the prevention of motion sickness when it should be given at least 30 minutes before traveling and it is also used in combination with analgesics to treat migraine attacks[7].

Literature survey revealed that only few methods available for the estimation of ZPD and BUCZ alone, in combination with other drugs in dosage form or in other forms. Most of them are based on HPLC, LC-MS, TLC, Mass and UV-Visible, and Polarographic methods [6-26]. But there is no common method for the simultaneous determination of ZPD and BUCZ. The analytically useful functional groups in BUCZ and ZPD have not been fully exploited for designing suitable visible spectrophotometric methods and so still offer a scope to develop few more visible spectrophotometric methods with better sensitivity, selectivity, precision and accuracy. Hence there is a need to develop sensitive and flexible visible spectrophotometric methods which prompted the author to carry out in this accord.

The author has developed a simple and sensitive spectrophotometric method by dissolving the drug Chloroform for the determination of ZPD, BUCZ in pure or pharmaceutical formulations (tablets) and adopted it as a reference method to compare the results obtained by proposed method.

METERIALS AND METHOD

Instrumentation: Spectral and absorbance measurements were made with digital Elico UV-Vis spectrophotometer SL 159 and pH measurements were made with Digisun Electronics digital pH meter model DI-707.

Reagents: All the chemicals and reagents were of analytical grade and the freshly prepared solutions were always used in the investigations.

ARS reaction (0.2 %, 5.84×10^{-3} M): 200 mg of Alizarin Red S dissolved in 100 ml distilled water. 0.1 N HCI solution was prepared by dissolving 8.6 ml of Conc. HCl and diluted to in 100 ml with distilled water

Working standard drug solutions: ZPD HCl (100 mg) was accurately weighed and dissolved in minimum amount of 0.1N HCl followed by dilution to 100 ml with distilled water in standard flask and this stock solution was diluted step wise with double distilled water to get the working standard solution of concentration of 25 µg/ml. Buclizine as hydrochloride was prepared by dissolving an appropriate amount of its salt (Buclizine Hydrochloride) equivalent to 100 mg of free base in 20 ml of water, adding 10 ml of 0.1 M NaOH solution and extracting the separated base with chloroform (4 × 20 ml). The combined chloroform extract was washed with water, dried over anhydrous sodium sulphate and made upto 100 ml with chloroform and this stock solution was diluted step wise with chloroform to get the working standard solutions of 50 µg/ml

Method: Into a series of 125 ml separating funnels containing aliquots of standard ZPD and BUZ solutions 6.0 ml of 0.1 M HCl solution and 2.0 ml of 0.2 % dye solution (ARS) were added successively. The total volume of aqueous phase in each separating funnel was adjusted to 15.0 ml with distilled water. To each separating funnel 10.0 ml of chloroform was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated chloroform layer was measured at λmax 420 nm against a similar reagent blank. This method involves the formation of ion-association complex between ZPD, BUZ and ARS. In order to establish the optimum conditions necessary for rapid and quantitative formation of the colored product with maximum stability and sensitivity, the author performed control experiments by measuring absorbance at 420 nm of a series of solutions, varying one and fixing the other parameters in each case such as type and volume of acid, concentration of dye, organic solvent used for extraction, ratio of organic phase to aqueous phase during extraction, shaking time and temperature.

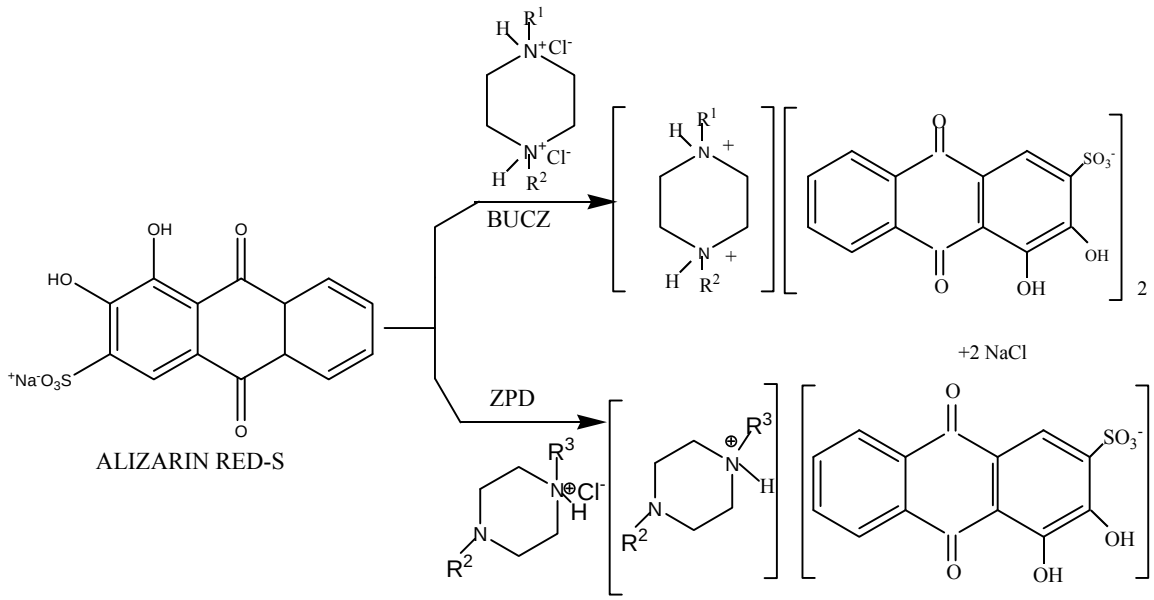
For pharmaceutical formulations: The method has also been applied to pharmaceutical formulations. An accurately weighed portion of tablet content equivalent to about 100 mg of ZPD and BUZ was transferred into a 100 ml volumetric flask. Added about 80 ml of warm isopropyl alcohol (ZPD) and $CHCl_3$ (BUCZ) and shaken well for about 20 minutes. The contents were diluted with isopropyl alcohol and chloroform upto the mark and mixed thoroughly. The solutions were filtered. The filtrates were evaporated to dryness. The residues were used for the preparation of formulation solutions for the method as given under standard solutions preparations. These solutions were analyzed as under procedures described from bulk solutions.

Reference method for ZPD[6]: An accurately weighed portion of the powdered tablets equivalent to 100 mg of drug was dissolved in 30 ml of isopropyl alcohol, shaken well and filtered and the filtrate was diluted to 100 ml with isopropyl alcohol to get 1 mg/ml solution of drug in formulations. 5 ml of this solution was further diluted to 200 ml to get 25 µg/ml solution. The absorbance of the solution was determined at λ_{max} 229 nm. The quantity of the drug was computed from the Beer's law plot of the standard drug in isopropyl alcohol.

Reference method for BUCZ[27]: An accurately weighed portion of the powdered tablets equivalent to 100 mg of drug was dissolved in 30 ml of chloroform, shaken well and filtered. It was evaporated to dryness. The residue was dissolved in chloroform. Solution was diluted to 100 ml with chloroform to get 1mg/ml. The above solution was further diluted to with chloroform to get 75 µg/ml solution. The absorbance of the solution was determined at λ_{max} 272 nm. The quantity drug was computed from the Beer's law plot of the standard drug in Chloroform.

RESULTS AND DISCUSSION

ZPD and BUCZ possess a tertiary amine and secondary groups. It forms an ion association complex with an acid dye (ARS) which is extractable into isopropanol/chloroform from aqueous phase. The protonated nitrogen (positive charge) of ZPD and BUCZ as hydrochloride is expected to attract the appositely charged part (negative charge) of the dye and behave as a single unit being held together by electrostatic attraction. It is supported by slope-ratio method. Based on the analogy, the structures of ion – association complexes are shown in scheme 1. $N\text{-}R^3$ has been preferred over $N\text{-}R^2$ as the former is more basic than the latter.



Scheme 1

Validation of method: The optimum conditions for the color development of method was established by varying the parameters one at a time, keeping the others fixed and observing the effect produced on the absorbance of the colored species (Table 1). The optical characteristics such as Beer's law limits, absorption maxima, molar absorptivity, and Sandell's sensitivity are presented in Table 2. The regression analysis using the method of least squares was made for the slope (b), intercept (a) and correlation (R) obtained from different concentrations and the results are summarized in Table 2. The percent relative standard deviation and percent range of errors (0.05 level and 0.01 confidence limits) were calculated for the two methods and the results are given in Table 2. The values obtained for the determination of ZPD and BUCZ in tablets by the proposed and UV methods are compared in Table 2. To evaluate the validity and reproducibility of the method, known amounts of pure drug were added to previously analyze pharmaceutical preparations and the mixtures were analyzed by the proposed methods. The percent recoveries are given in Table 3.

CONCLUSIONS

The developed UV spectrophotometric method for the estimation of ZPD and BUCZ was found to be simple and useful with high accuracy, precision, and reproducible. Sample recoveries in all formulations using the above methods were in good agreement with their respective label claim or theoretical drug content, this suggesting the validity of the method and non interference of formulation excipients in the estimation.

REFERENCE

[1] Mahir Alkan, Myroslava Kharun and Fedor Chmilenko. Spectrophotometric determination of molybdenum with Alizarin Red S in the presence of poly(sulfonylpiperidinylmethylene hydroxide), Talanta, 2003:;59 (3): 605-611
[2] Hernández-Méndez J, Carabias-Martínez R, B. Moreno-Cordero and Gutiérrez-Dávila L.Spectrophotometric determination of aluminium with alizarin red S sensitized with poly vinyl pyrrolidone, Analytica Chimica Acta, 1983; 149: 379-383
[3] Homayon Ahmad Panahi, Meghdad Karimi, Elham Moniri, Hamidreza Soudi Development of a sensitive spectrophotometric method for determination of copper, African Journal of Pure and Applied Chemistry, 2008; 2 (10): 096-099.
[4] Srikanth K, Emmanuel KA, Ramesh Raju K. Spectrophotometric determination of oxybutynin chloride through ion-association complex formation, Rasayan J.Chem., 2010; 3 (1): 179-187
[5] Basavaiah K, SriLatha, Swamy JM. Spectrophotometric determination of ceterizine hydrochloride with Alizarin Red S, Talanta, 1999; 50 (4):887-92.
[6] Medikondu Kishore, Hanumantharao Y. A Validated Spectrophotometric methods for the determination of Ziprasidone as Hydrochloride in Bulk and pharmaceutical formulations: International Journal of Chemical and Analytical Science, 2010; 1(7):151-153
[7] Srinubabu G, Sudha Rani B, Seshagiri Rao JVLN. Spectrophotometric determination of ziprasidone in pharmaceutical formulations.E-journal of chemistry. 2006; 3 (10): 9-12.
[8] Anand Kumar Y, Anitha M, Hemanth A, Srinivas S. Development of rapid UV spectrophotometric method for the estimation of ziprasidone hydrochloride in bulk and formulations; Digest journal of nanomaterials and biostructures, 2010; 5(1): 279 – 283
[9] Pankaj K, Choudhary P. Development and validation of spectrophotometric method for the estimation of ziprasidone HCl, Oriental Journal of Chemistry 2006; 21:101-5.
[10] Sudha Rani B, Venkata Reddy P, Estimation of Ziprasidone Hydrochloride Monohydrate in Bulk and Capsules by Reverse Phase HPLC, E-Journal of Chemistry 2006; 3: 169-172.

[11] Sachse J, Härtter S. Automated determination of ziprasidone by HPLC with column switching and spectrophotometric detection, Ther Drug Monit, 2005;27: 158-62.
[12] Zhang G, Simultaneous determination of five antipsychotic drugs in rat plasma by high performance liquid chromatography with ultraviolet detection, J Chromatogr B Analyt Technol Biomed Life Sci 2007; 856: 20-8.
[13] El-Sherif ZA. Stability indicating reversed-phase highperformance liquid chromatographic and thin layer densitometric methods for the determination of ziprasidone in bulk powder and in pharmaceutical formulations, Biomed Chromatography, 2004; 18:143-149.
[14] Aravagiri M, Pollock B. Determination of ziprasidone in human plasma by liquid chromatography-electrospray tandem mass spectrometry and its application to plasma level determination in schizophrenia patients, J Chromatogr B Analyt Technol Biomed Life Sci 2007; 847: 237-44.
[15] Aravagiri M, Marder SR. Analytical technologies in the biomedical and life sciences, Determination of ziprasidone in human plasma by liquid chromatography-electrospray tandem mass spectrometry and its application to plasma level determination in schizophrenia patients. Journal of chromatography, 2006; 847: 122-6.
[16] Zhang G, Bartlett MG. Liquid chromatography/tandem mass spectrometry method for the simultaneous determination of olanzapine, risperidone, 9-hydroxyrisperidone, clozapine, haloperidol and ziprasidone in rat plasma. Rapid Commun Mass Spectrum, 2007; 21: 920-8.
[17] Al Dirbashi. Rapid liquid chromatography-tandem mass spectrometry method for quantification of ziprasidone in human plasma, Biomedical Chromatography, 2006; 20: 4-8.
[18] Kirchherr H. Quantitative determination of forty-eight antidepressants and antipsychotics in human serum by HPLC tandem mass spectrometry: a multi-level, single-sample approach, J Chromatogr B Analyt Technol Biomed Life Sci.,2006; 843: 100-113.
[19] Janiszewski J, Schneider RP. Mass spectrometry method for quantification of ziprasidone in human plasma. Mass Spectrom, 1997; 11: 1033.
[20] Abdel Fattah M, El Walily, Alaa, El Gindy, Abdel Aziz M, Wahbi. A Spectrophotometric Method for the Determination of Buclizine Hydrochloride Using the Charge-Transfer Spectrum of Buclizine-Iodine Complex: Spectroscopy Letters, 1996; 29 (2): 217 – 230
[21] Annapurna V, Jyothi G, Nagalakshmi V, Sailaja BBV. Spectrophotometric determination of Buclizine as hydrochloride (BUCZ) using I_2/PMAP-SAc, AM/PTC and PMA/cobalt(II)/EDTA, Journal of the Indian Chemical Society,.2009; 86:358-363
[22] Farhan Ahmed Siddiqui, Agha Zeeshan Mirza, M. Hashim Zuberi and Faiza Qureshi Optimization of quantitative analysis of buclizine hydrochloride using UV spectrophotometry in bulk drug and dosage formulations, Medicinal Chemistry Research. INPRESS (DOI-10.1007/s00044-009-9286-5).2010
[23] Vitthal D, Dhakane, Milind B.Ubale. A Validated Stability-Indicating HPLC Assay Method for Buclizine Hydrochloride in Bulk Drug and Dosage Form: Analytical chemistry- An Indian Journal, 2009; 8(4): 1-5.
[24] Muhammad S, Arayne, Najma Sultana, Farhan A. Siddiqui. Simultaneous Determination of Pyridoxine, Meclizine and Buclizine in Dosage Formulations and Human Serum by RP-LC, Chromatographia. 2008; 67(11-12): 941-945.
[25] Arayne MS, Sultana N, Mirza AZ, Siddiqui FA. Simultaneous Determination of Gliquidone, Fexofenadine, Buclizine, and Levocetirizine in Dosage Formulation and Human Serum by RP-HPLC, J Chromatogr Sci.,2010; 48(5): 382-5.
[26] Arayne MS, Sultana N, Siddiqui FA. Quantitation of buclizine hydrochloride in pharmaceutical formulations and human serum by RP-HPLC. Pak J Pharm Sci., 2006; 19 (4):326-9.
[27] Medikondu Kishore, Surendrababu K, Kalyani Ch S R G, Janardhan M. Optimization of Quantitative Analysis of Buclizine Hydrochloride Using Spectrophotometry In Bulk Drug and Pharmaceutical Formulations. International Journal of Current Pharmaceutical Research 2010; 2(4): 48-51

Table 1: Optimum conditions established in method for ZPD & BUCZ

Parameter	Optimum range	Conditions in procedure	Remarks
λ_{max} (nm)	410-430	420	
Effect of acid on colour development	0.08 - 0.12 HCl	0.1M HCl	Variation of molarity of acid beyond the upper and lower limits resulted in low absorbance values
Effect volume of for ARS for (5.8×10^{-3}M)	1.0 - 3.0 ml	2.0 ml	2.0 ml dye solution of was necessary for covering broad range of Beer's law limits
Choice of organic solvent for extraction of the colored complex	$CHCl_3$	$CHCl_3$	The water immiscible solvents tested for the extraction of the colored complex into organic phase which include (chlorobenzene, carbontetrachloride, benzene, n-butanol and chloroform). Chloroform was preferred for its selective extraction of the colored drug-dye complex from the aqueous phase
Effect of ratio of organic to aqueous phase on extraction	1:1.5	1:1.5	The extraction of the colored species into organic layer was incomplete when the ratio of organic to aqueous phase was more than the specified ratio in each case
Effect of shaking time on extraction	1 - 5 min	2 min	Constant absorbance values were obtained for shaking periods between 1-5 min.
Effect of temperature on the colored species	Laboratory temperature ($28\pm3^{\circ}C$)	Laboratory temperature	At low temperature ($< 20^0$C) the extraction of colored species was found to be improper. At high temperature ($>35^0$C) the stability of the colored species was found to be less.
Stability of the colored species in organic solvent.	1 - 60 min	5 min	

Table 2: Optical and regression characteristics, precision and accuracy of the proposed method

Parameter	**ZPD**	**BUCZ**
λ_{max} (nm)	420	420
Beer's law limits (μg/ml)	2.5-15.0	2.5-15.0
Detection limit (μg/ml)	7.0517	0.2019
Molar absorptivity (1/mol.cm)	1.715×10^{4}	1.999×10^{4}
Sandell's sensitivity (μg/cm^2/0.001 absorbance unit)	9.104×10^{-2}	8.620×10^{-2}
Optimum photometric range (μg/ml)	6 – 14	7-15
Regression equation (Y=a + bc)		
slope (b)	0.03984	0.04098
Standard deviation on slope (S_b)	1.016×10^{-2}	3.205×10^{-4}
Intercept (a)	3.999×10^{-3}	1.5×10^{-3}
Standard deviation on intercept (S_a)	8.424×10^{-2}	2.658×10^{-3}
Standard error on estimation (S_e)	8.038×10^{-2}	2.536×10^{-3}
Correlation coefficient (r)	0.9997	0.9999
Relative standard deviation (%) *	0.6644	0.8326
% Range of error (confidence limits)		
0.05 level	0.763	0.9573
0.01 level	1.198	1.501

* Average of six determinations considered

Table 3: Assay of ZPD & BUCZ in Pharmaceutical Formulations

Formulations*	Amount taken (mg)	Amount found by proposed Method**		Percentage recovery by proposed methods***		
	ZPD/ BUCZ	ZPD	BUZ	Reference method (ZPD/BUCZ)	ZPD	BUZ
Tablet I	60/25	59.69±0.68 F = 1.489 t = 0.43	24.68±0.51 F = 2.048 t =0.7821	59.88±0.83 24.96±0.73	99.93±0.41	99.73±0.61
Tablet II	60/25	60.05±0.51 F=1.47 t = 0.86	24.63±0.43 F = 2.285 t = 0.8980	60.12±0.78 24.91±0.65	99.73±0.61	99.83±0.33
Tablet III	60/25	59.73±0.59 F=1.747 t = 0.986	24.59±0.32 F = 2.540 t = 1.210	59.93±0.46 24.88±0.51	99.83±0.35	99.65±0.91
Tablet IV	60/25	59.81±0.39 F=1.388 t = 0.489	24.72±0.31 F= 2.2018 t = 1.124	59.88±0.83 24.97±0.46	99.85±0.31	99.83±0.90

* Tablets from four different pharmaceutical companies.
** Average ± standard deviation of six determinations, the t-and F-test values refer to comparison of the proposed method with the reference method. Theoretical values at 95% confidence limit, F = 5.05, t = 2.57
***Recovery of 10 mg added to the pre-analyzed pharmaceutical formulations (average of three determinations).